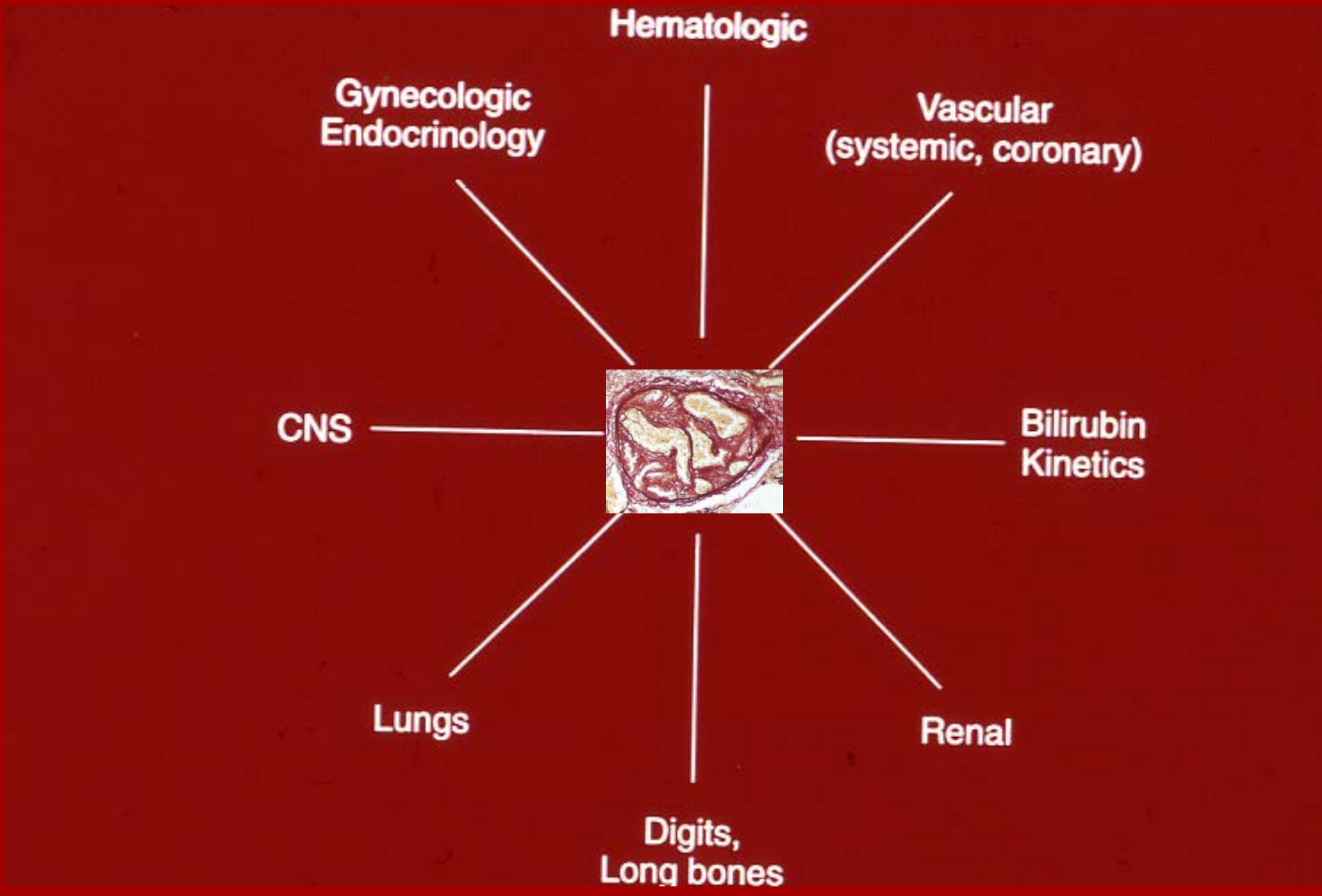
CCHD - A Multi-System Systemic Disorder



ACVIM FORUM
As far as you want to go.

Joseph K. Perloff

I have the following disclosures* related to my presentation:

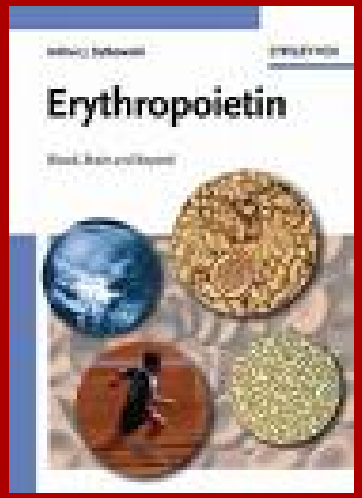
Employee:	**n/a**
Grants/Research Contracts:	**n/a**
Consulting:	**n/a**
Investments:	**n/a**

I will discuss results of clinical trial for the following agents that are currently NOT approved for use in animals.

***Disclosures include spouse and immediate family where relevant.**

Hematologic Disorders

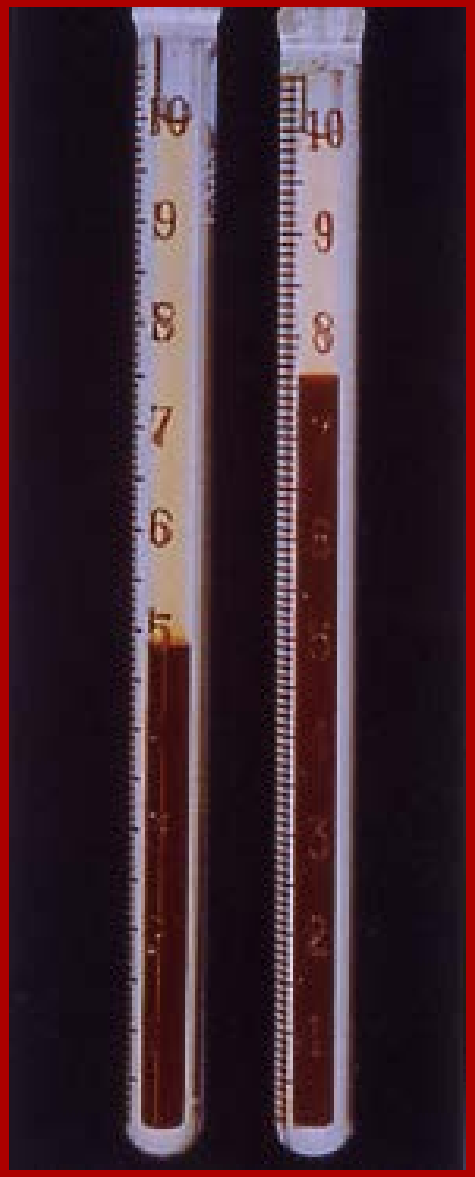
Why Does Red Cell Mass Increase in Cyanotic Congenital Heart Disease?



A decrease in tissue oxygenation provokes renal release of erythropoietin and an increase in red cell mass that is a desirable compensatory adaptation to systemic arterial hypoxemia.

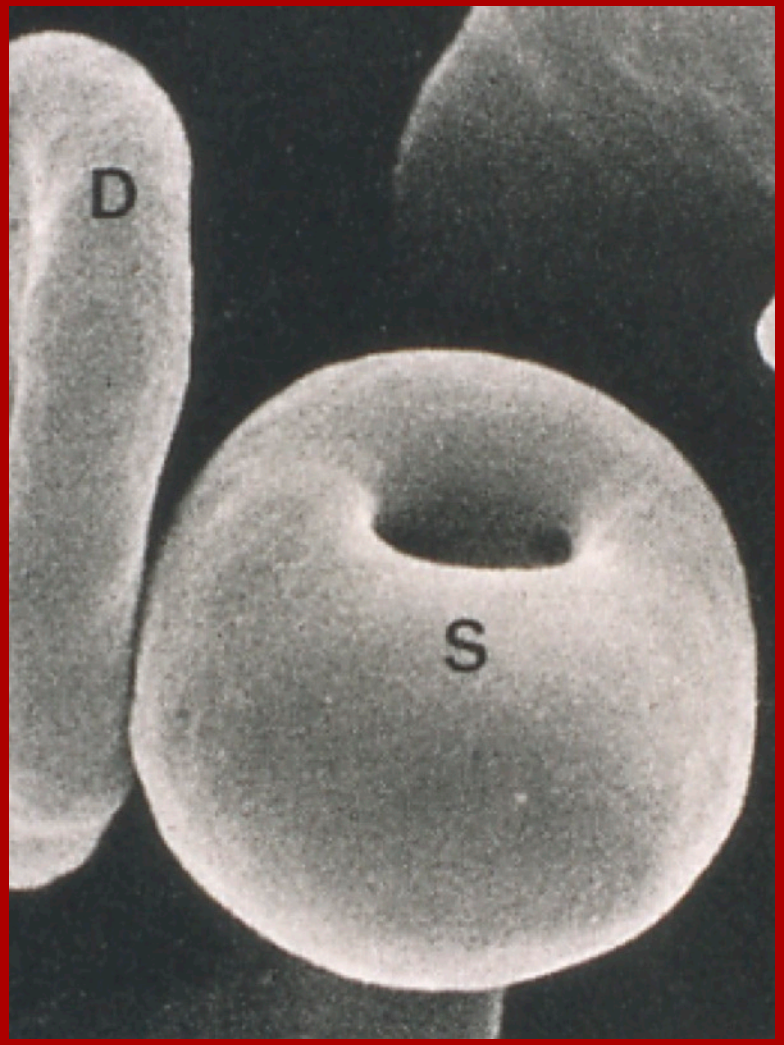
Blood Letting
A Therapeutic Anachronism

Phlebotomy reduces red cell mass, reduces oxygen delivery to metabolizing tissues, stimulates a maladaptive release of erythropoietin, and results in undesirable iron deficiency.

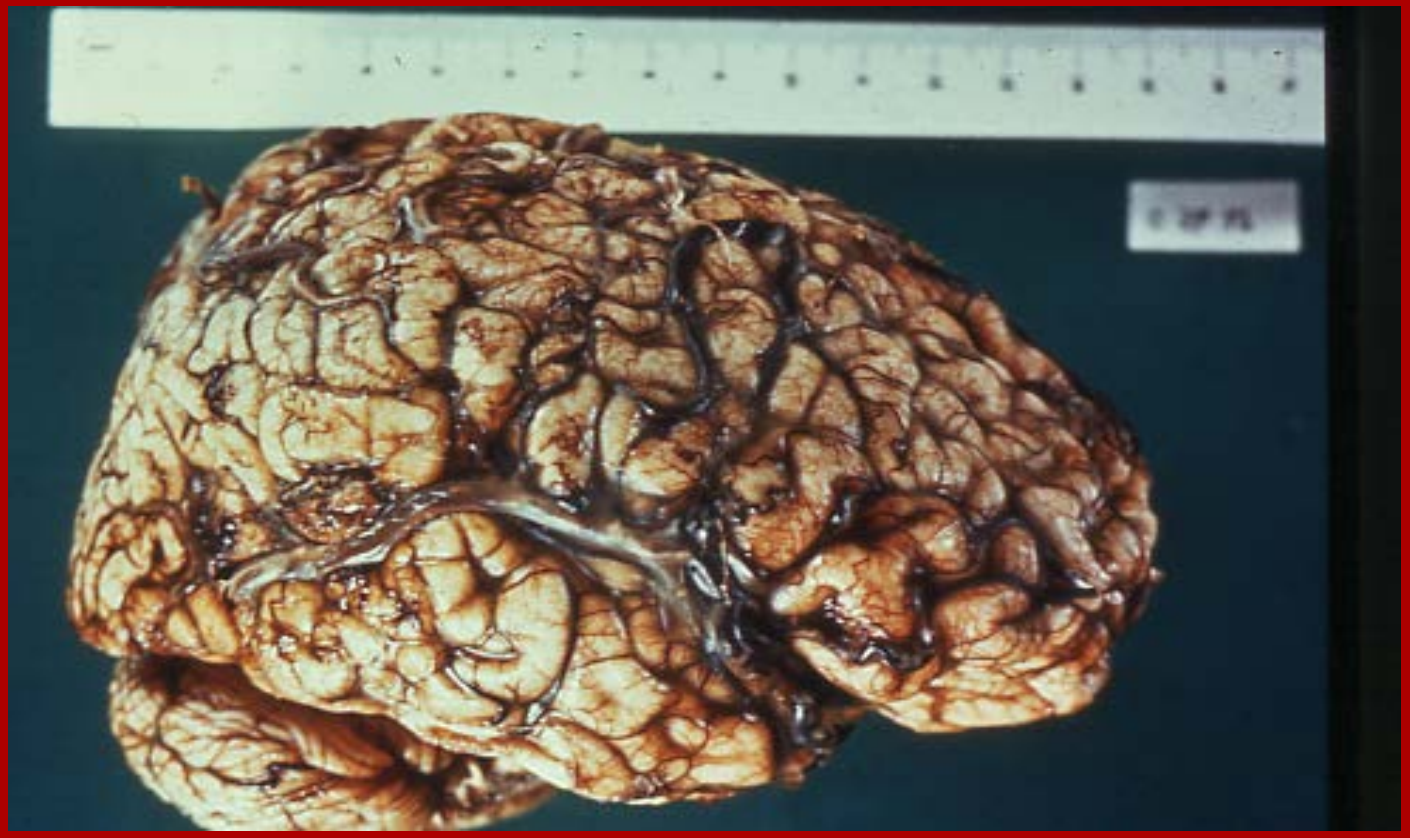


Hematocrit only by automated electronic particle counter

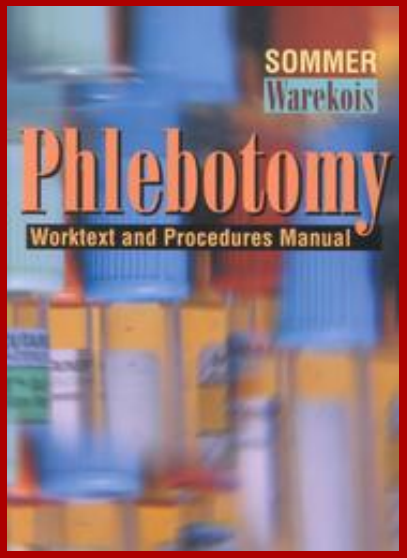
Whole blood viscosity increases when deformable biconcave disc become non-deformable iron deficient microspherocytes.



Iron deficient erythrocytosis in infants predisposes to stroke due to cerebral *venous* thrombosis.



Criteria for Phlebotomy



1. Not based on hematocrit irrespective of level because erythrocytosis is not a risk factor for stroke due to cerebral arterial thrombosis.
2. Employed for temporary relief of significant hyperviscosity symptoms.
3. The amount of blood removed is the minimum required to achieve relief of hyperviscosity symptoms, generally one unit with isovolumetric saline replacement.
4. Hydroxyurea blunts the erythropoietin rebound.

Hemostasis in Cyanotic Congenital Heart Disease

"The temptation to use the anticoagultant drugs may be great. On the basis of the present studies, their use would appear to be fraught with danger."

Robert C. Hartmann
Johns Hopkins 1952

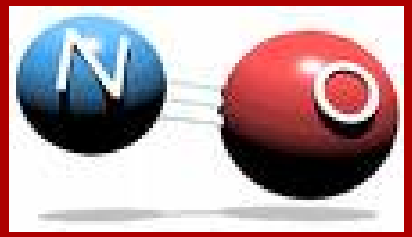
Intrinsic hemostatic defect(s) and *increased tissue vascularity in response to nitic oxide* predispose to hemorrhage.

Erythrocytosis, whether iron replete or iron deficient, *is not a risk factor for stroke* due to cerebral arterial thrombosis

Preoperative Phlebotomy

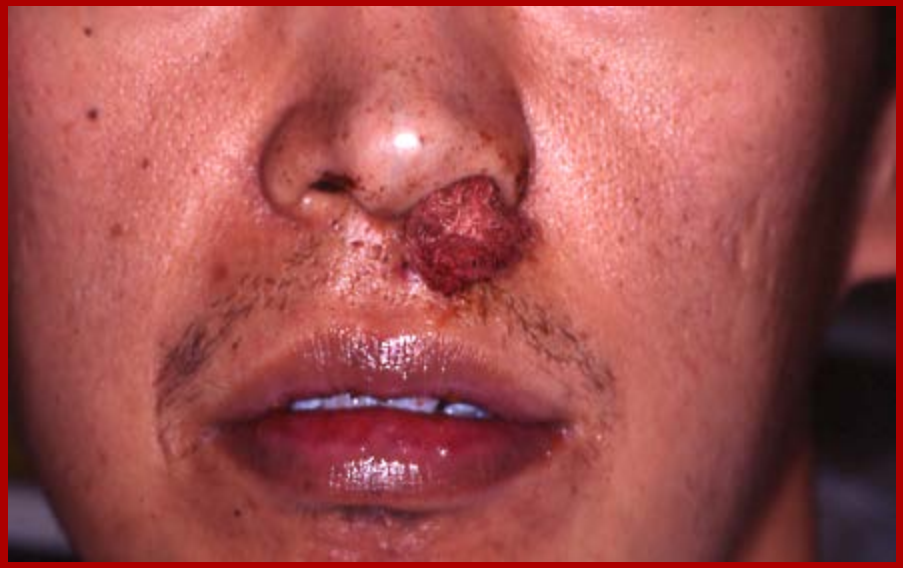
Whole blood is removed isovolumetrically in daily amounts of 500ml to reduce the hematocrit to just below 65%. Within hours, platelet counts rise, and platelet aggregation and hemostasis improve.

Nitric Oxide and Oxyhemoglobin



The increased endothelial shear stress of erythrocytosis stimulates release of NO that diffuses luminally to enter red blood cells and enhance release of oxygen from oxyhemoglobin, and diffuses adluminally to enter medial smooth muscle cells and promote vasodilatation and increased tissue vascularity.

Epistaxis



Spontaneous:

a) Intrinsic hemostatic defect(s)

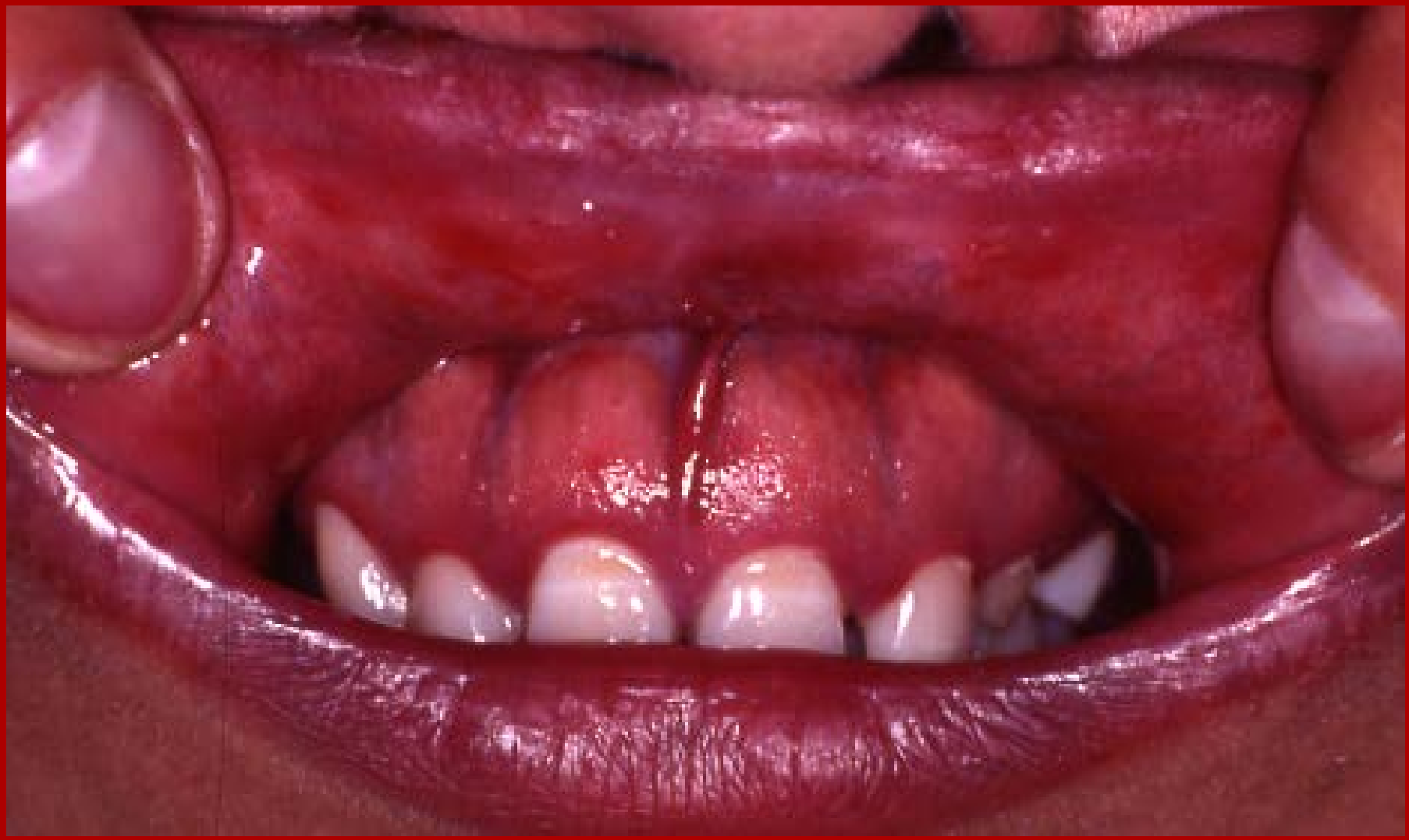
b) Increased nasal mucous membrane vascularity

Induced:

a) Traumatic

b) Drying effect of non-humidified nasal O_2

Tissue Response to TGF ß and PDGF



There's something ominous about blood coming from the mouth like the glow of fire.

Anton Chekhov about himself

Pulmonary Hemorrhage in Eisenmenger Syndrome

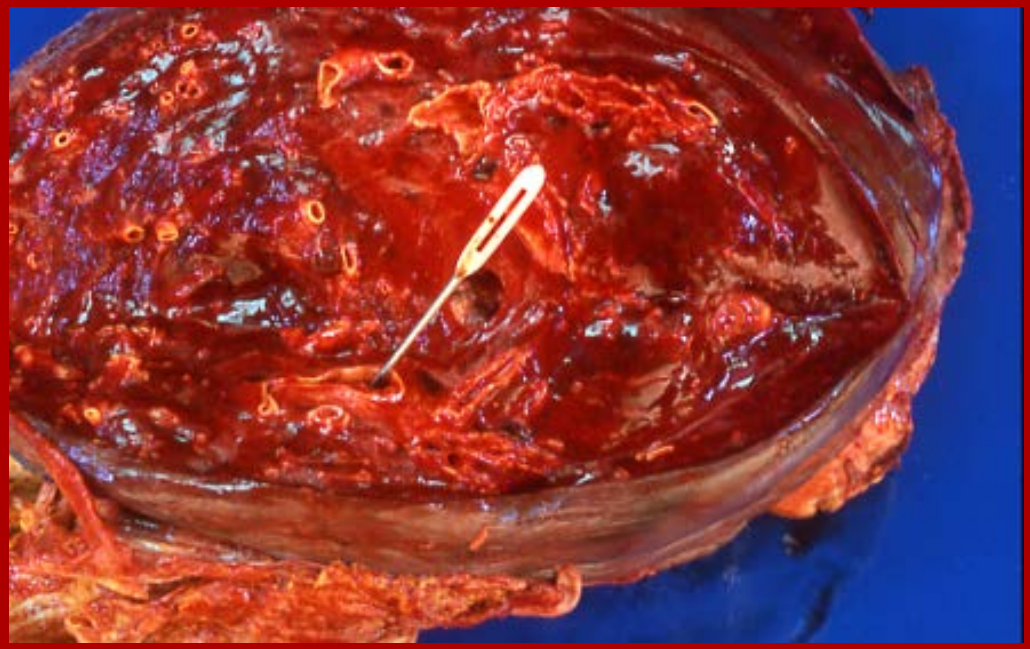
Hemoptysis
(Extrapulmonary Hemorrhage)

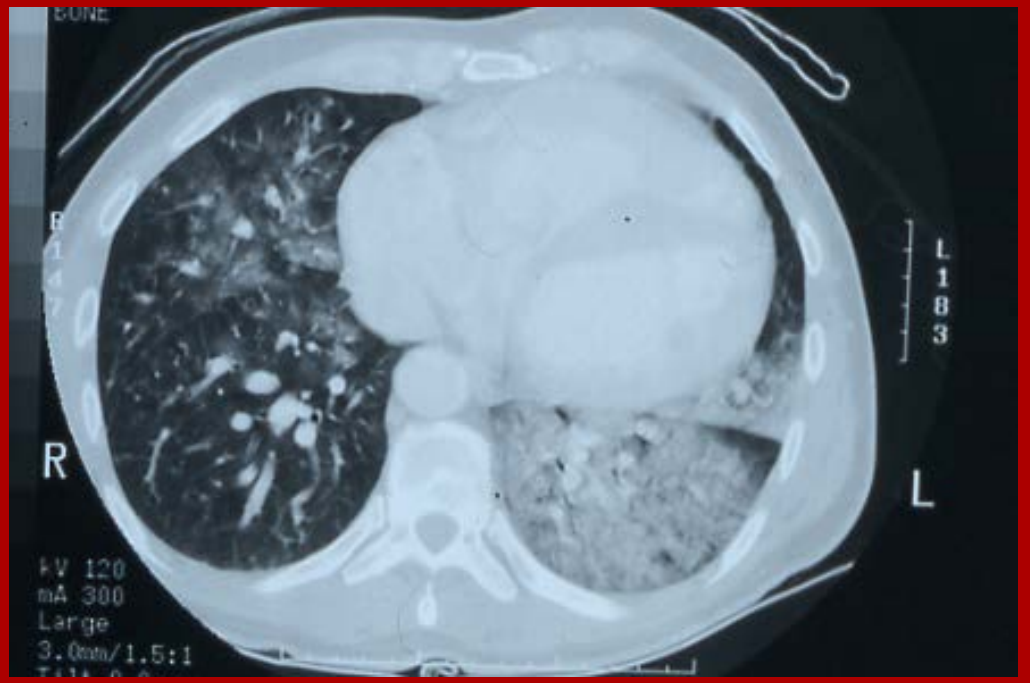
"The histology showed hemorrhagic lung."

Victor Eisenmenger, 1897

Intrapulmonary Hemorrhage

A common cause of sudden death in Eisenmenger syndrome





Management of Hemoptysis in Eisenmenger Syndrome

1. Do not bronchoscope:
2. History—of an antiplatelet or anti-inflammatory agent ?
3. Chest x-ray for detection of intrapulmonary hemorrhagic infilrates.
4. CT scan if infiltrates are present
5. Hospitalize for all but mild or moderate intrapulmonary hemorrhage

Treatment of Intrapulmonary Hemorrhage

1. Normal Platelet Counts:
   Fresh frozen plasma
2. Thrombocytopenia--platelet transfusion,
   cryoprecipitate.
3. Excessively low hematocrit---blood transfusion.

Catamenial Hemoptysis

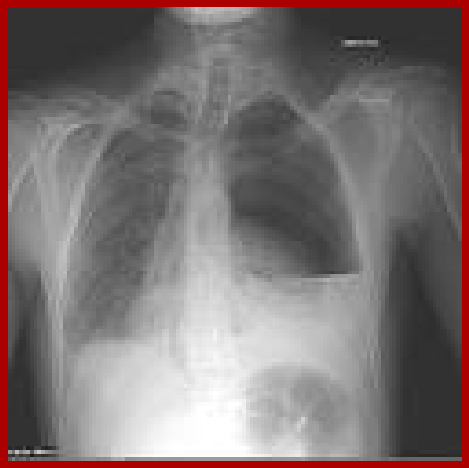
Pulmonary Endometriosis

Hemoptysis that coincides with menses. Rupture of capillaries within endometrial epithelium in the lumen of muscular pulmonary arteries.

Endometrial epithelium (brackets)
lining the lumen of a muscular pulmonary artery.

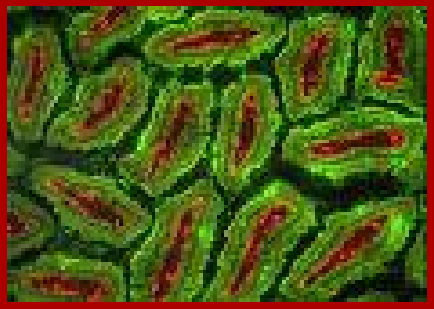
Catamenial Pneumothorax

Pleural Endometriosis



Recurrent pneumothorax that coincides with the menstrual cycle as described by Maurer in 1958, and called catemenial pneumothorax by Lillington in 1972.

von Willebrand Factor in CHD

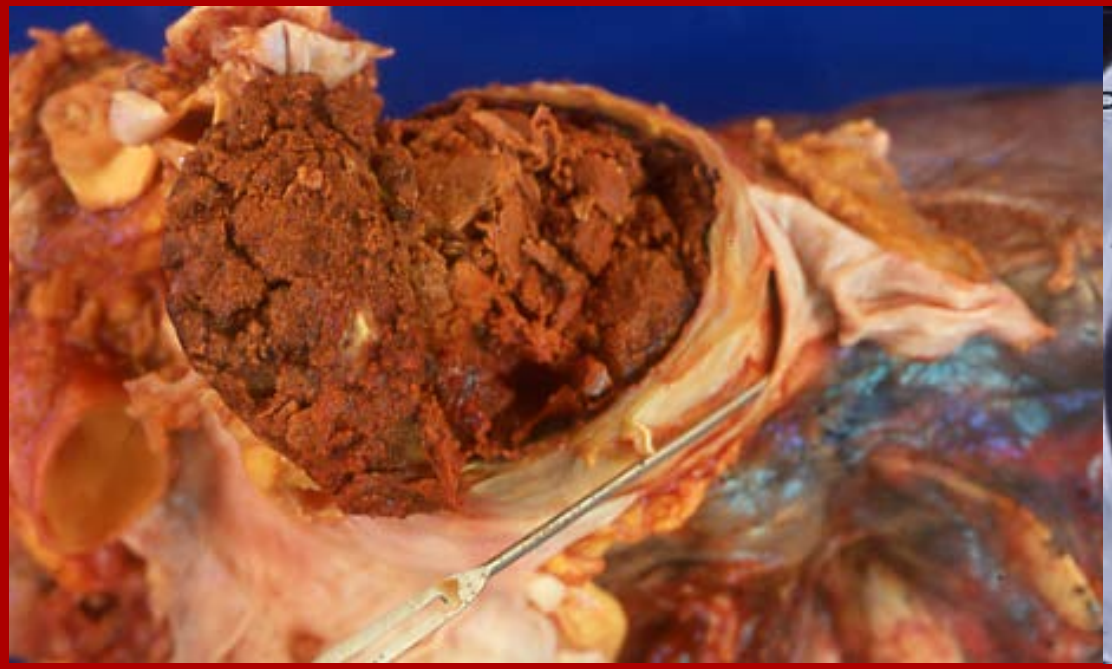


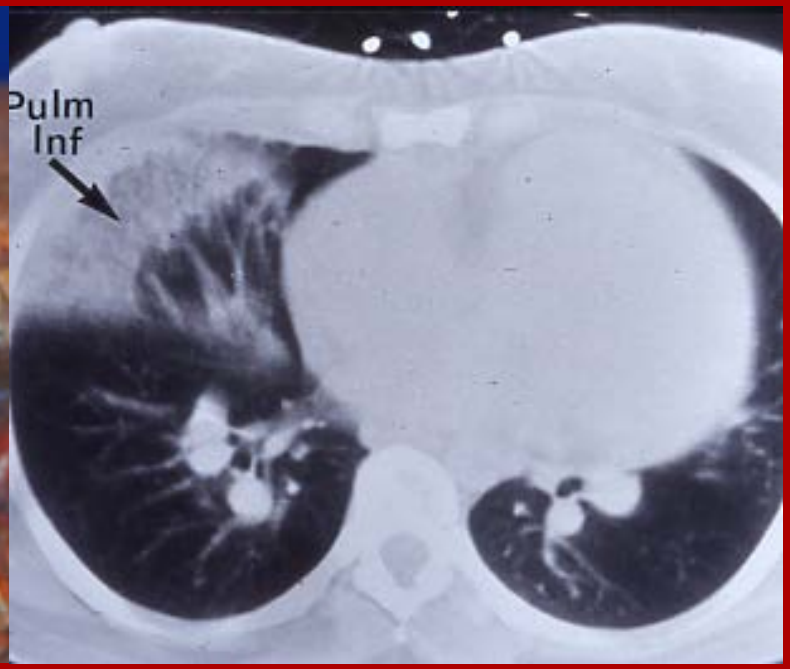
von Willebrand factor (red)
stored in endothelial cells (green)

A decrease in or loss of the largest vWF multimetric forms occurs in over 70% of CHD patients with pulmonary vascular disease, turbulent blood flow or cyanosis.

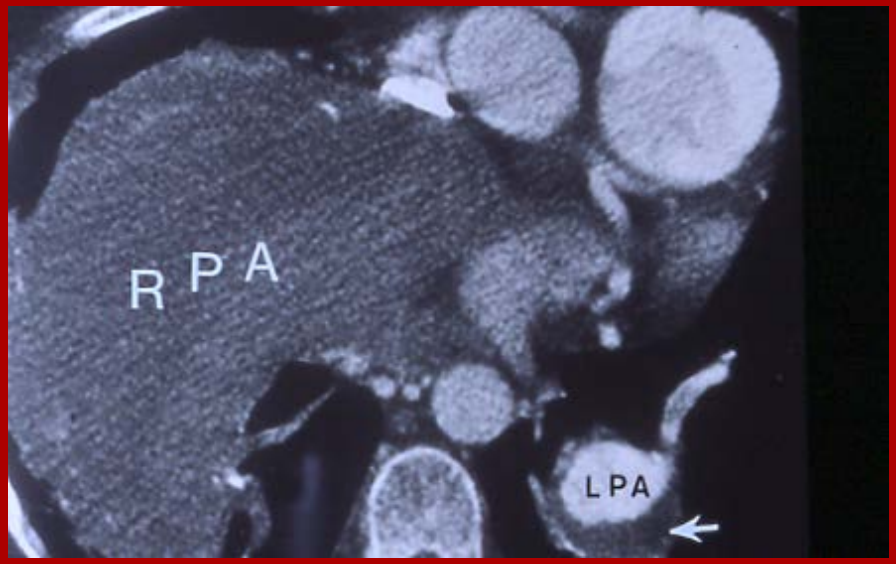
Agarose Gel Electrophoresis

Massive Intrapulmonary Thrombus



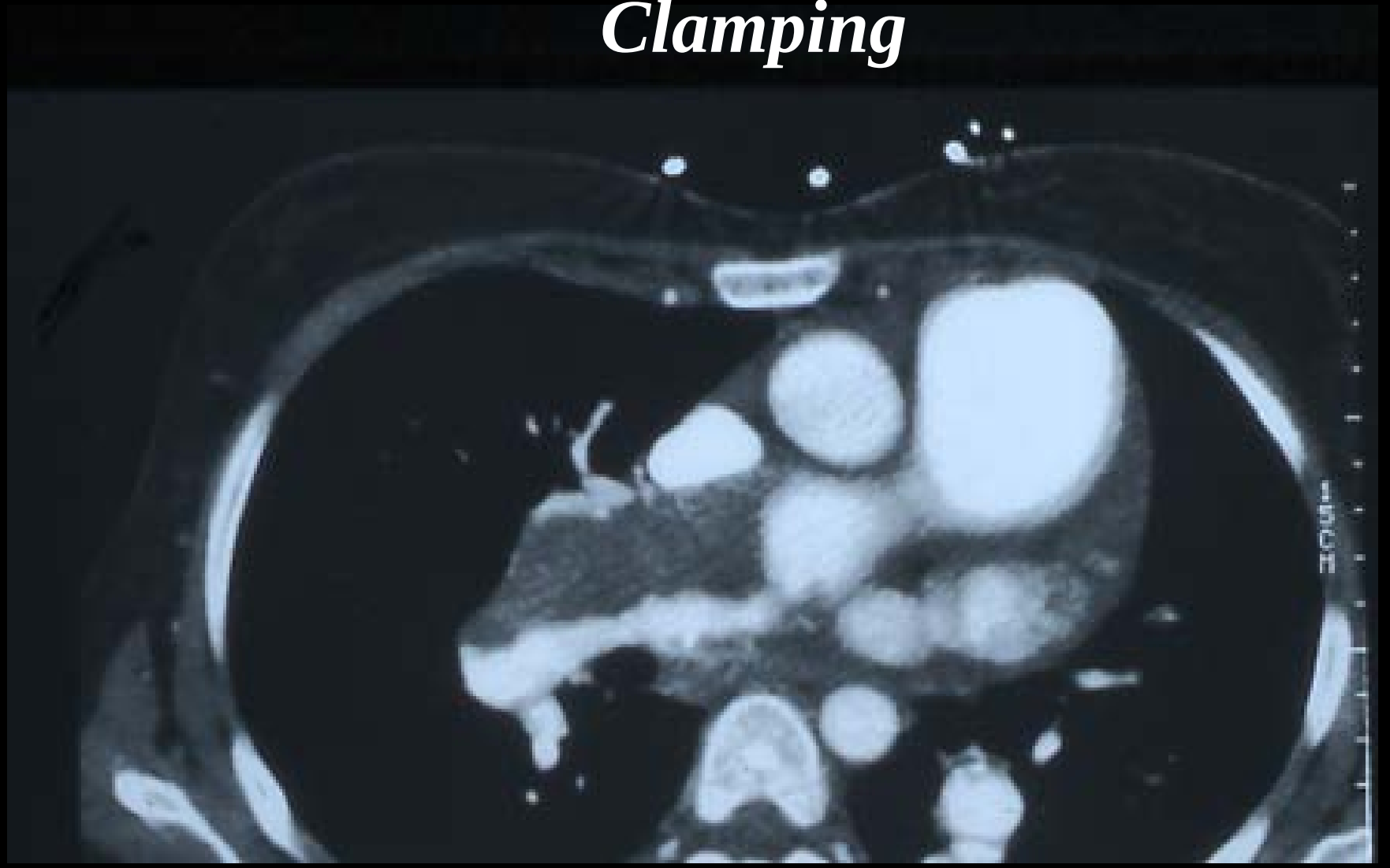


Thrombosis in Dilated Hypertensive Proximal Pulmonary Arteries A Therapeutic Dilemma

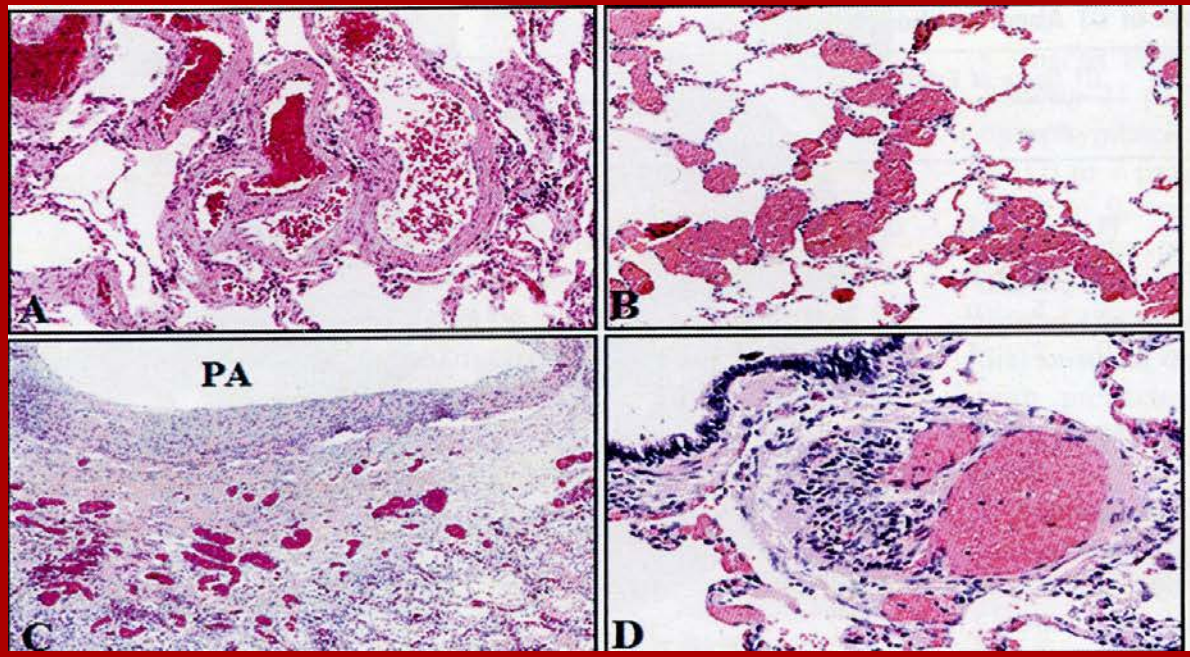


1. Anticoagulants--Efficacy is nil. Risk of aggrevating intrinsic hemostatic defects and provoking hemorrhage is high.
2. Thrombolytic Agents – Efficacy is nil even with intrapulmonary administration.

Lung Transplantation The Hazard of Cross Clamping



Pulmonary Neovascularity
A Distinctive Radiologic Feature of Eisenmenger Syndrome



Microscopic sections from a man with Eisenmenger syndrome and a nonrestrictive VSD. A, Clusters of dilated, tortuous, muscular arteries within alveolar septa, the latter of which were visible without magnification and resembled the neovessels observed on CT. B, Markedly dilated, congested capillaries within the alveolar tissues. C, A markedly dilated, vascular lesion consisting of congested capillaries within the adventitial tissue surrounding a medium-size, muscular, pulmonary artery (PA). These lesions differed distinctly from plexiform lesions of hypertensive pulmonary arteriopathy (D), with dilated channels and foci of prominent endothelial proliferation (all H&E stain, original magnifications: A=×100, B=×200, C=×40, D=×400.

A. Clusters of dilated, tortuous muscular arteries within alveolar septae.
B. Dilated congested capillaries within alveolar tissues.
C. Congested capillaries within adventitial tissue (PA--Medium-size muscular pulmonary artery).
D. Plexiform lesion of hypertensive pulmoary arteriopathy.

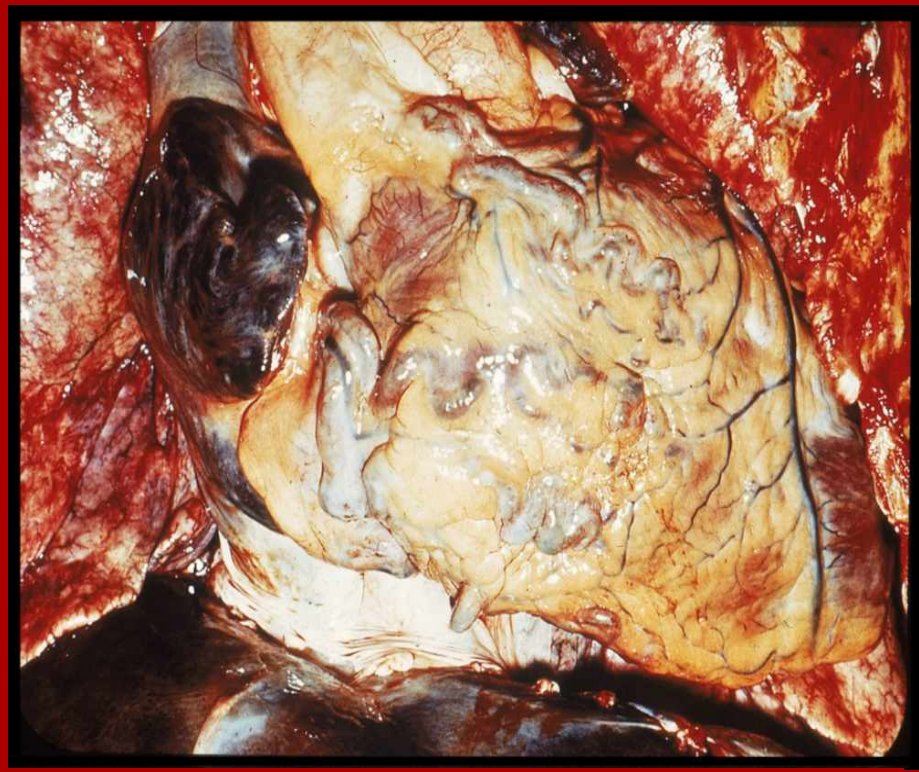
Coronary Circulation in Cyanotic Congenital Heart Disease

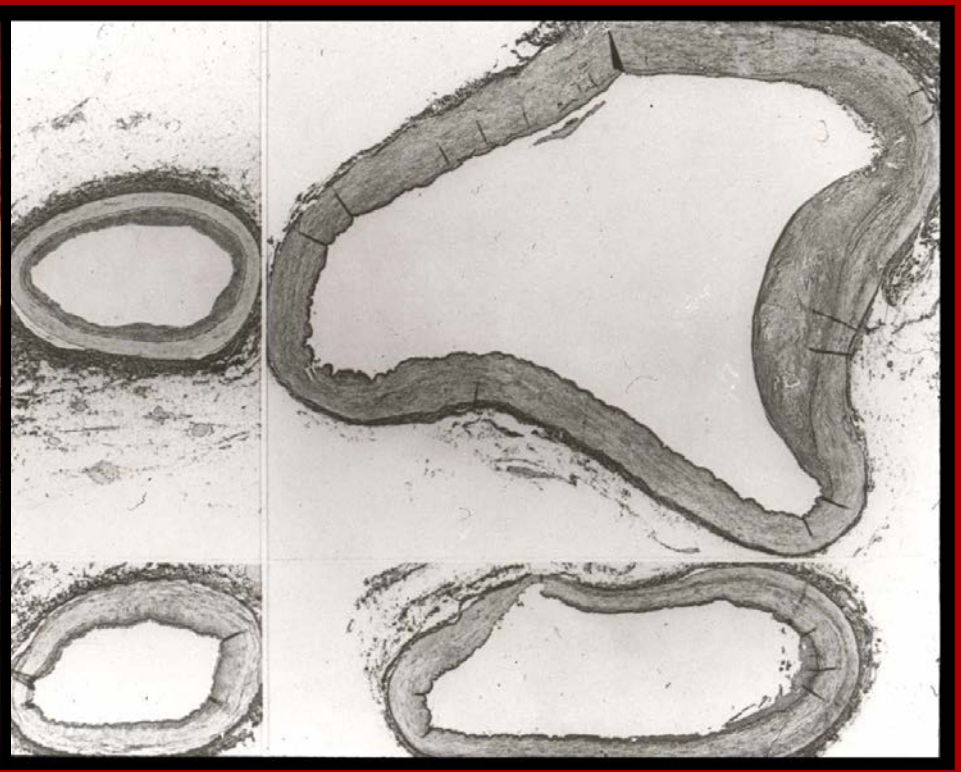
Dilatated tortuous extramural coronary arteries.

Basal coronary blood flow and myocardial flow reserve.

Coronary microcirculation.

Anti-atherogenic effects of CCHD.

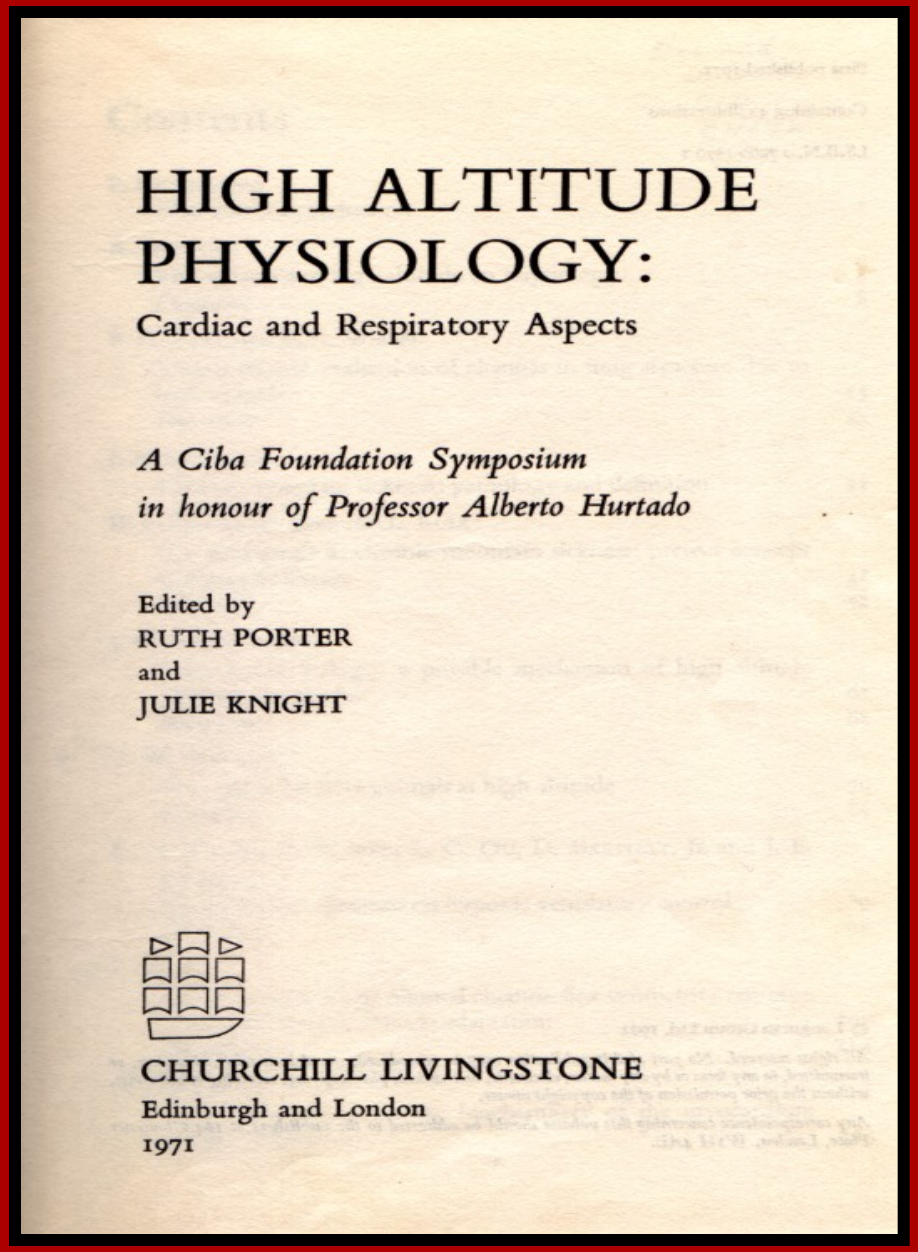




Aneurysmal Dilatation of the Coronary Arteries in Cyanotic Congenital Cardiac Disease

Perloff and Roberts

Am J Med 1968



HIGH ALTITUDE PHYSIOLOGY:

Cardiac and Respiratory Aspects

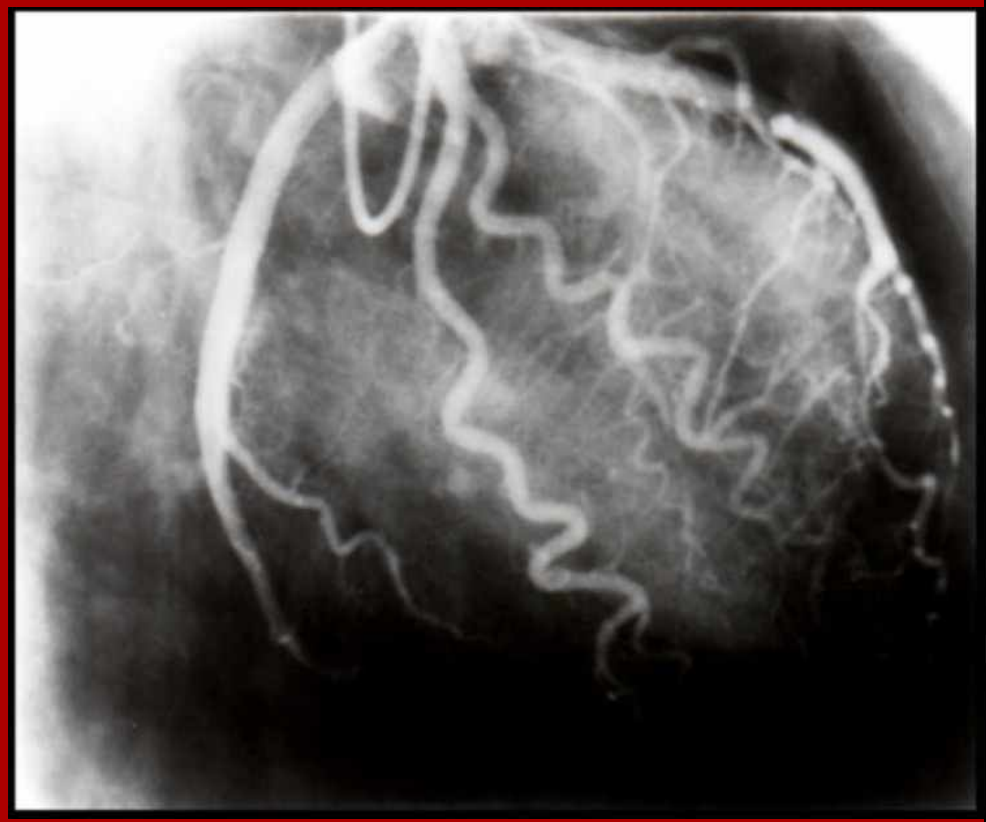
A Ciba Foundation Symposium
in honour of Professor Alberto Hurtado

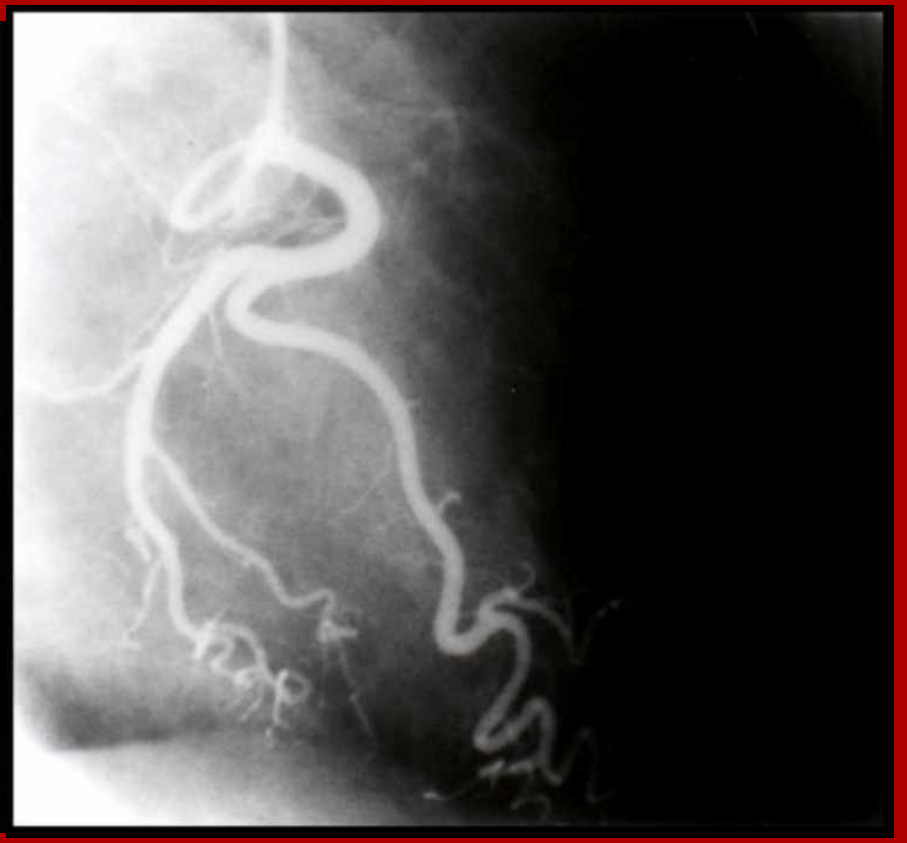
Edited by
RUTH PORTER
and
JULIE KNIGHT

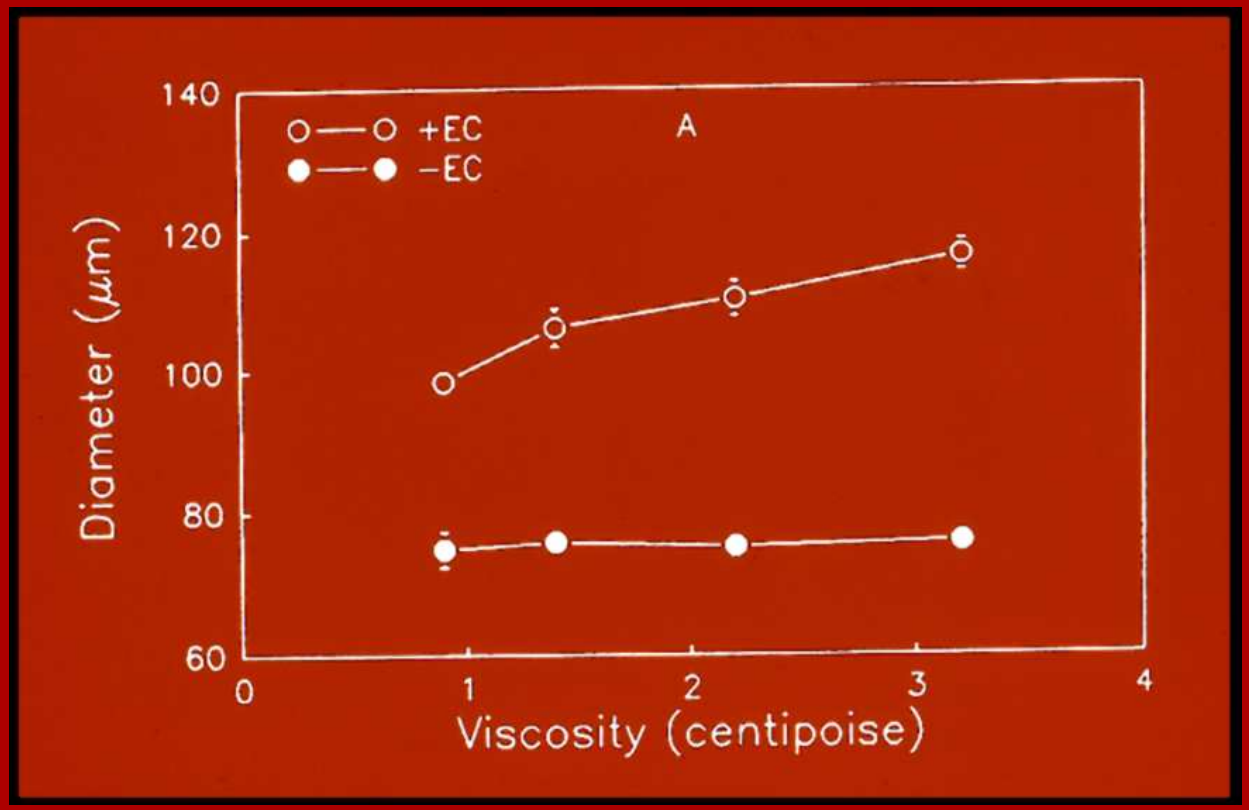
CHURCHILL LIVINGSTONE
Edinburgh and London
1971

Hypoxemic erythrocytotic adults acclimatized to high altitude have dilated tortuous extramural coronary arteries analagous to hypoxemic erythrocytotic adults with CCHD.

Moderately Dilated Tortuous Coronary Arteries in CCHD

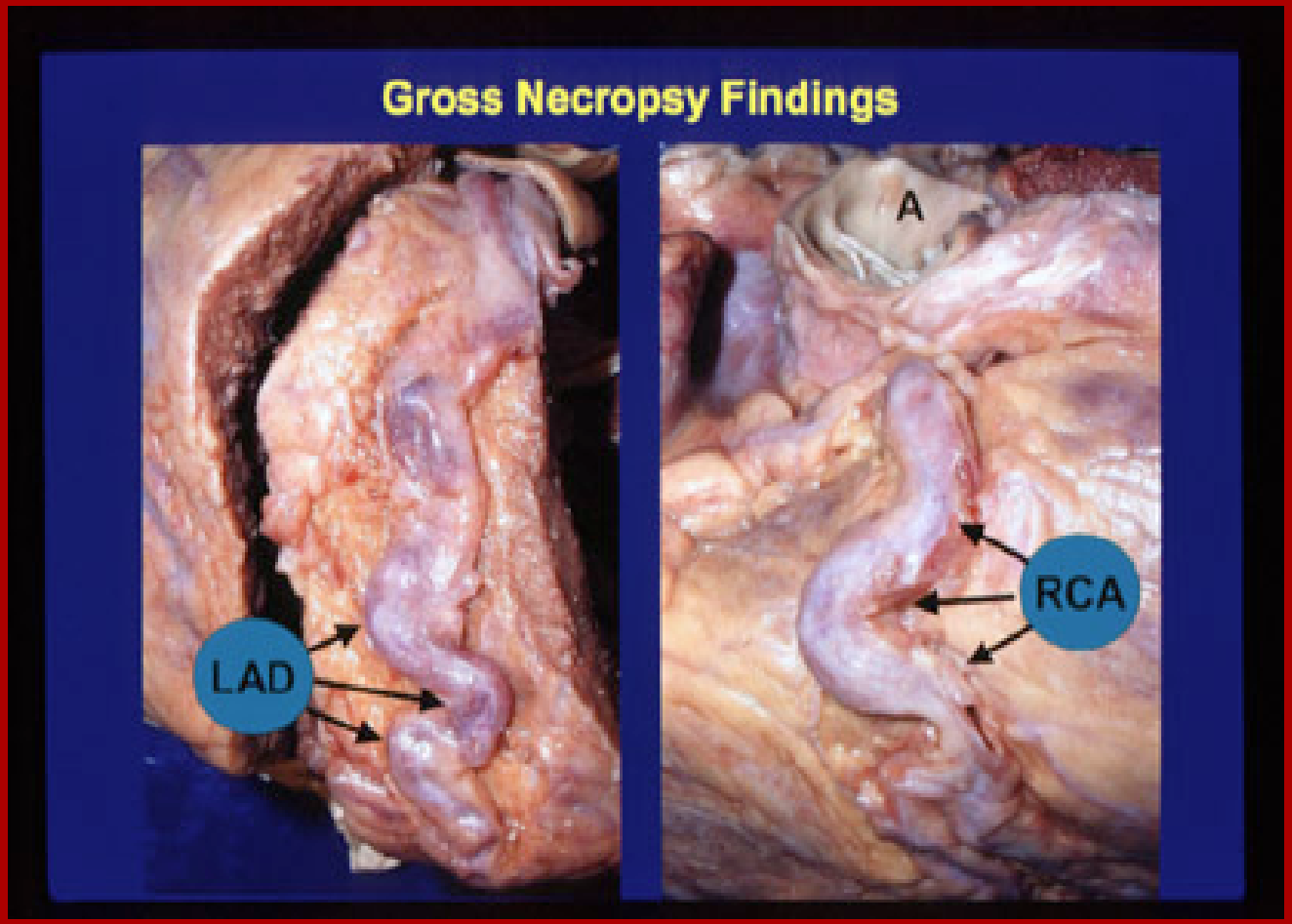




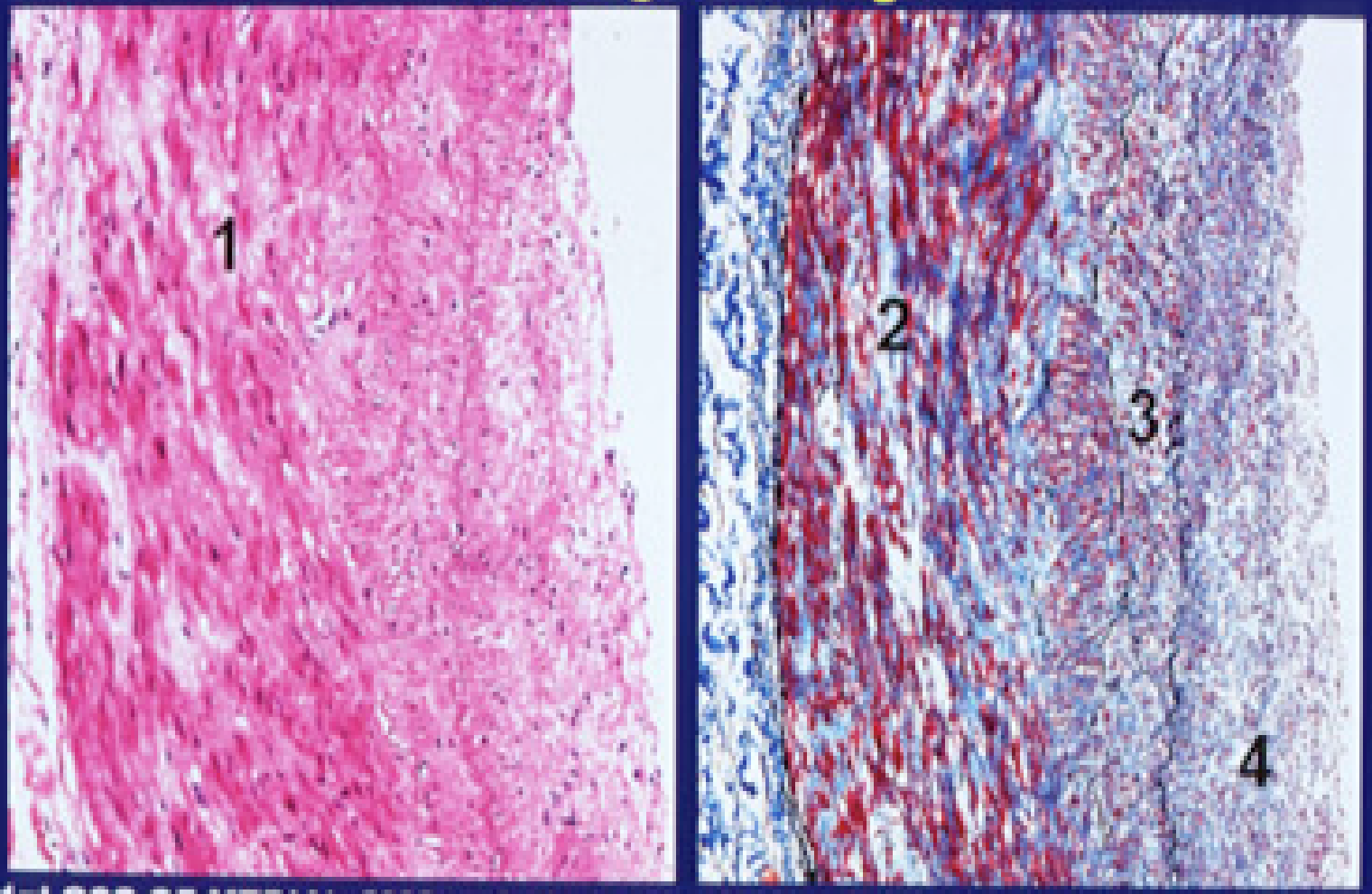


Increased endothelial shear stress caused by the viscous erythrocytotic perfusate in CCHD and high altitude provokes elaboration of NO and initiates dilatation of extramural coronary arteries.

However, dilatation exceeds the vasodilator effect because coexisting medial structural abnormalities cause mural attenuation



Histologic Findings



1=LOSS OF MEDIAL SMCs; 2=INCREASED MEDIAL COLLAGEN
3=DUPLICATION OF IEL; 4=FIBROMUSCULAR INTIMAL HYPERPLASIA

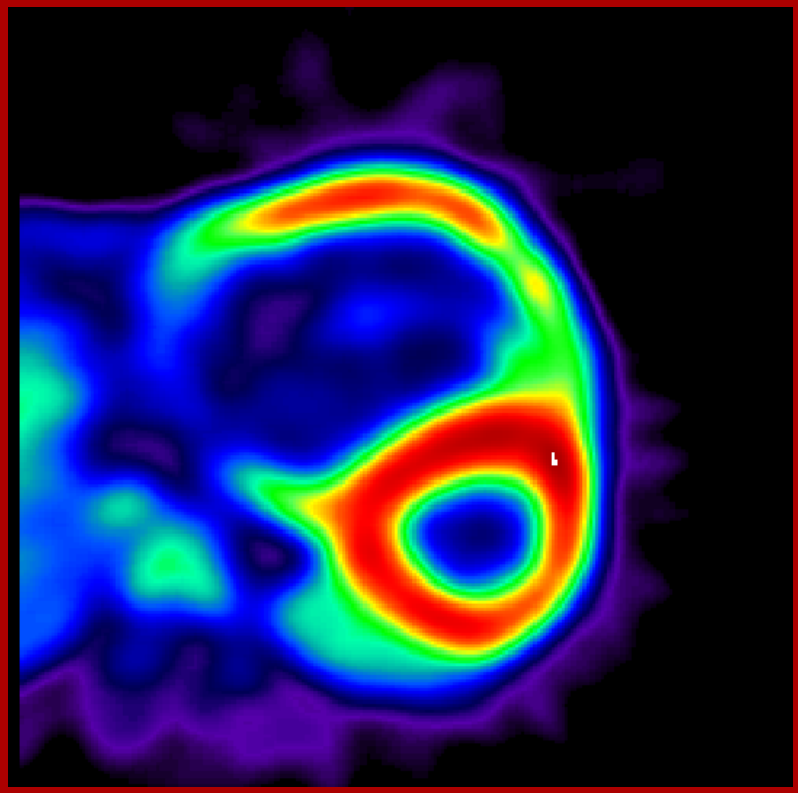
Basal Myocardial Blood Flow & Flow Reserve in CCHD

Systemic arterial hypoxemia reduces the oxygen content of blood entering the coronary circulation. The oxygen deficit cannot be corrected by an increase in myocardial oxygen extraction, because extraction is already maximal, or by increased coronary arterial dilatation because the extramural coronaries are already maximally dilated.

Coronary Flow and Flow Reserve in CCHD

***Basal flow* as determined by N-13 PET.**

***Flow reserve* as determined by pharmacologic stress induced with IV dipyridamole.**



32 year old cyanotic woman with an ASD and pulmonary vascular disease.

Despite increased basal flow, coronary flow reserve is not encroached upon because of remodeling of the microcirculation.

The Peruvian Andes

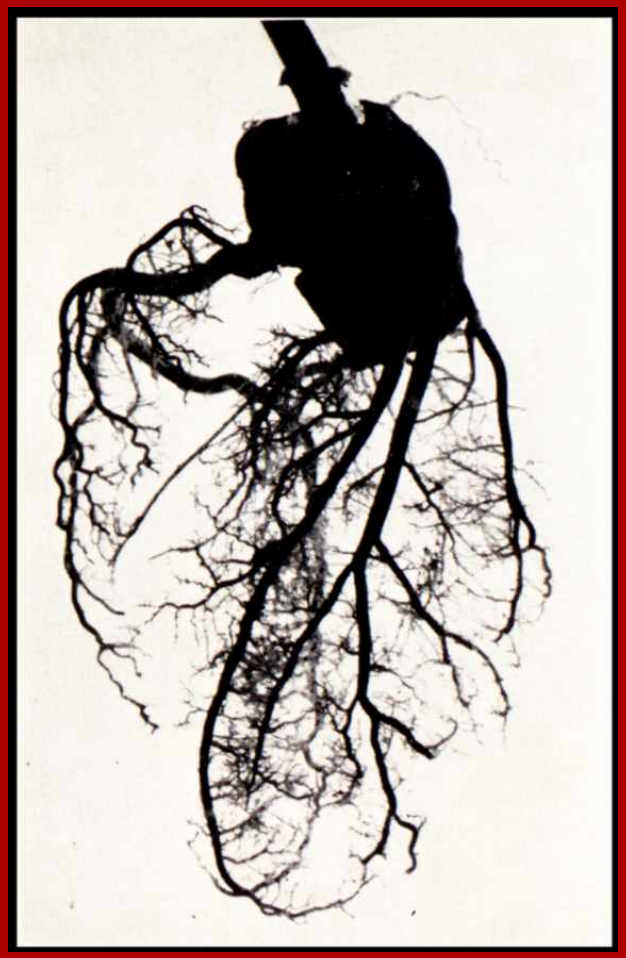
Peru

20,000 feet

ANATOMY OF THE CORONARY CIRCULATION AT HIGH ALTITUDE

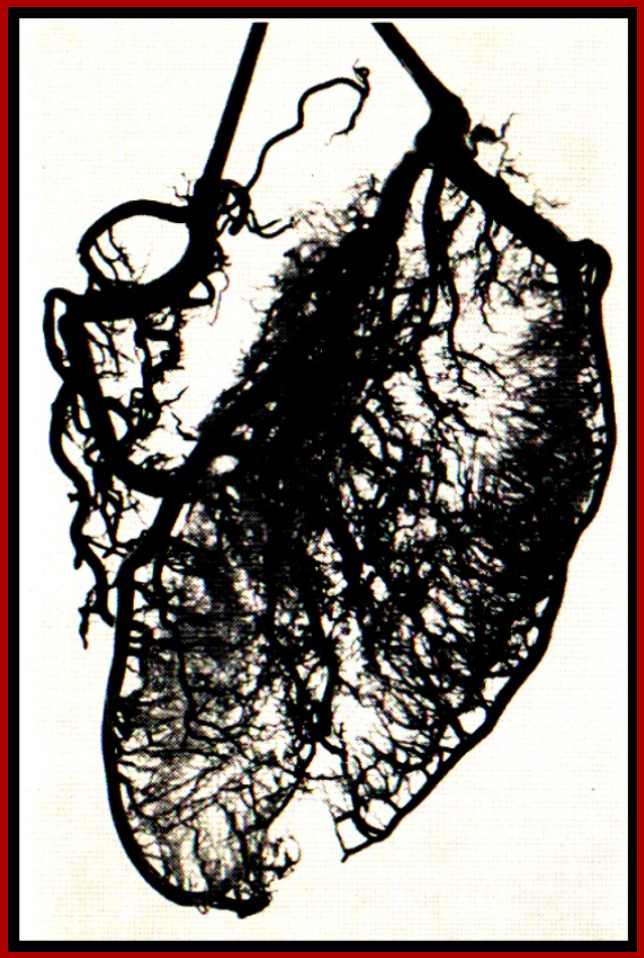
Arias-Stella and Topilsky

Peruvian Andes



Sea Level

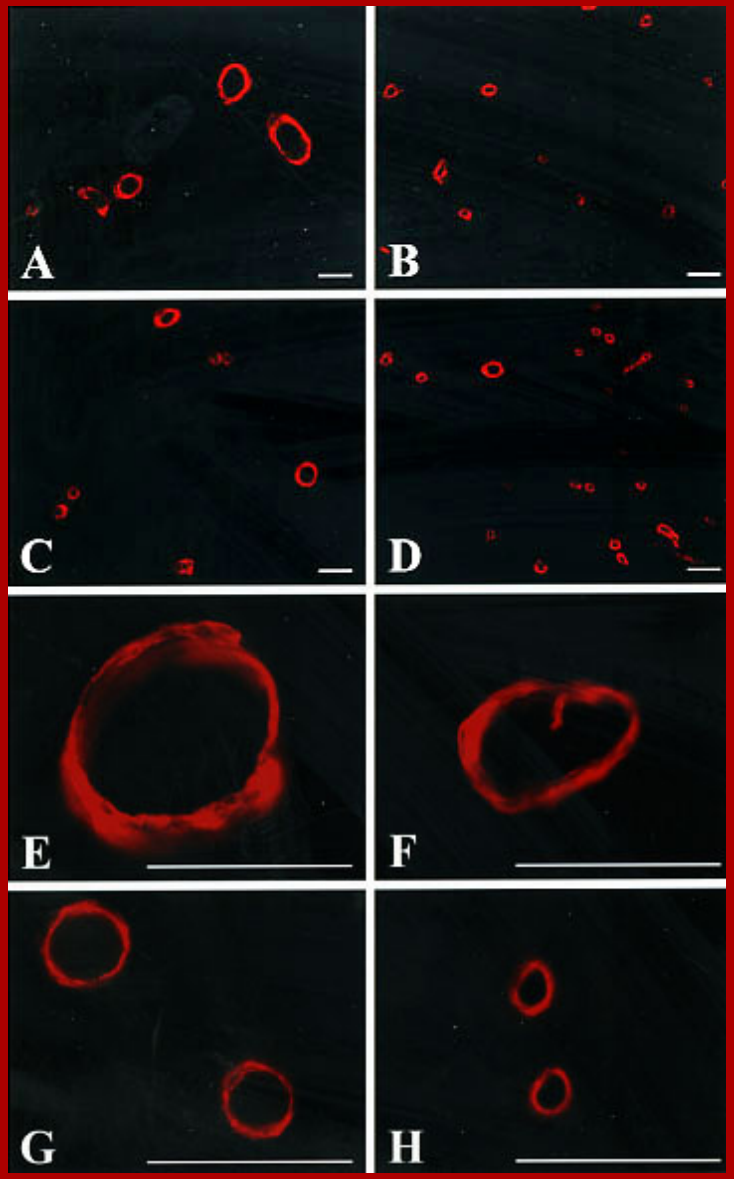
Acrylic resin casts



High Altitude

Morphometric analyses of coronary arterioles that are immunostained against SM alpha-actin.

Eisenmenger hearts (A/C): terminal arterioles are fewer in number compared to hypertrophied structurally normal hearts (B/D), but are greater in diameter (E/G).



A,C,E,G Eisenmenger hearts.
B,D,F,H structurally normal hearts with ventricular hypertrophy

Flow Reserve

Conclusions

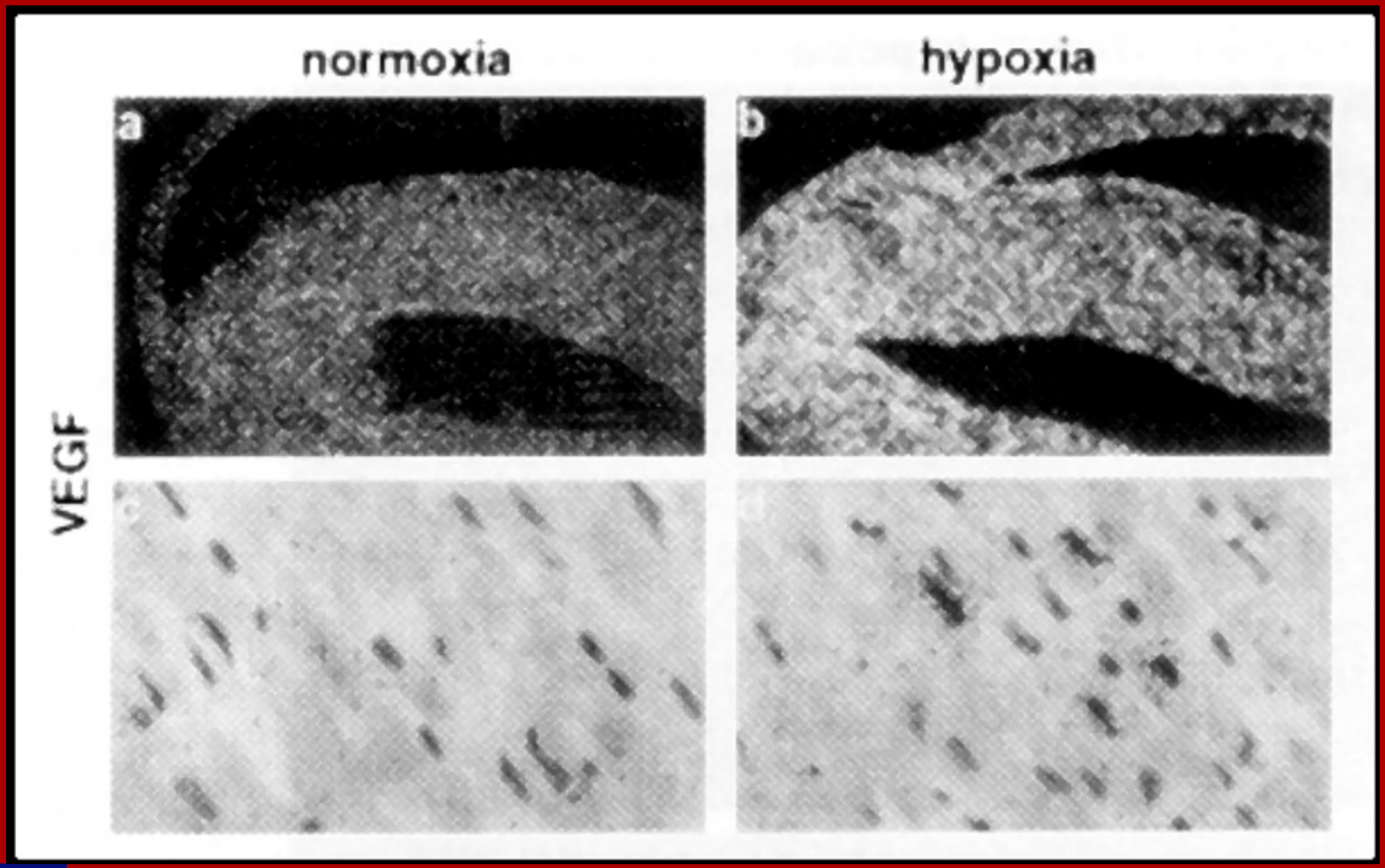
Remodeling of the coronary microcirculation is the key mechanism responsible for preservation of flow reserve in CCHD. Decreased length, volume and surface densities, and greater terminal arteriole diameters reflect remodeling, supplemented by enhanced vasodilatory capacity.

Systemic hypoxia changes the organ-specific distribution of vascular endothelial growth factor (VEGF) and its receptors.

Max Planck Institute, Krakow

- *VEGF, a homodimeric glycoprotein, plays a key role in physiological blood vessel formation and angiogenesis.*
- *Hypoxia induces a marked upregulation of VEGF and a marked increase in angiogenesis-related VEGF gene expression, stimulating new vessel growth.*

VEGEF



Coronary Atherogenesis in CCHD

No angiographic evidence of atherosclerosis compared to the general population with a decade-by-decade incidence of 4.5% to 13.5%.

No necropsy evidence of coronary atherosclerosis.

Paucity of Coronary Atherosclerosis: Variables

Hypocholesterolemia

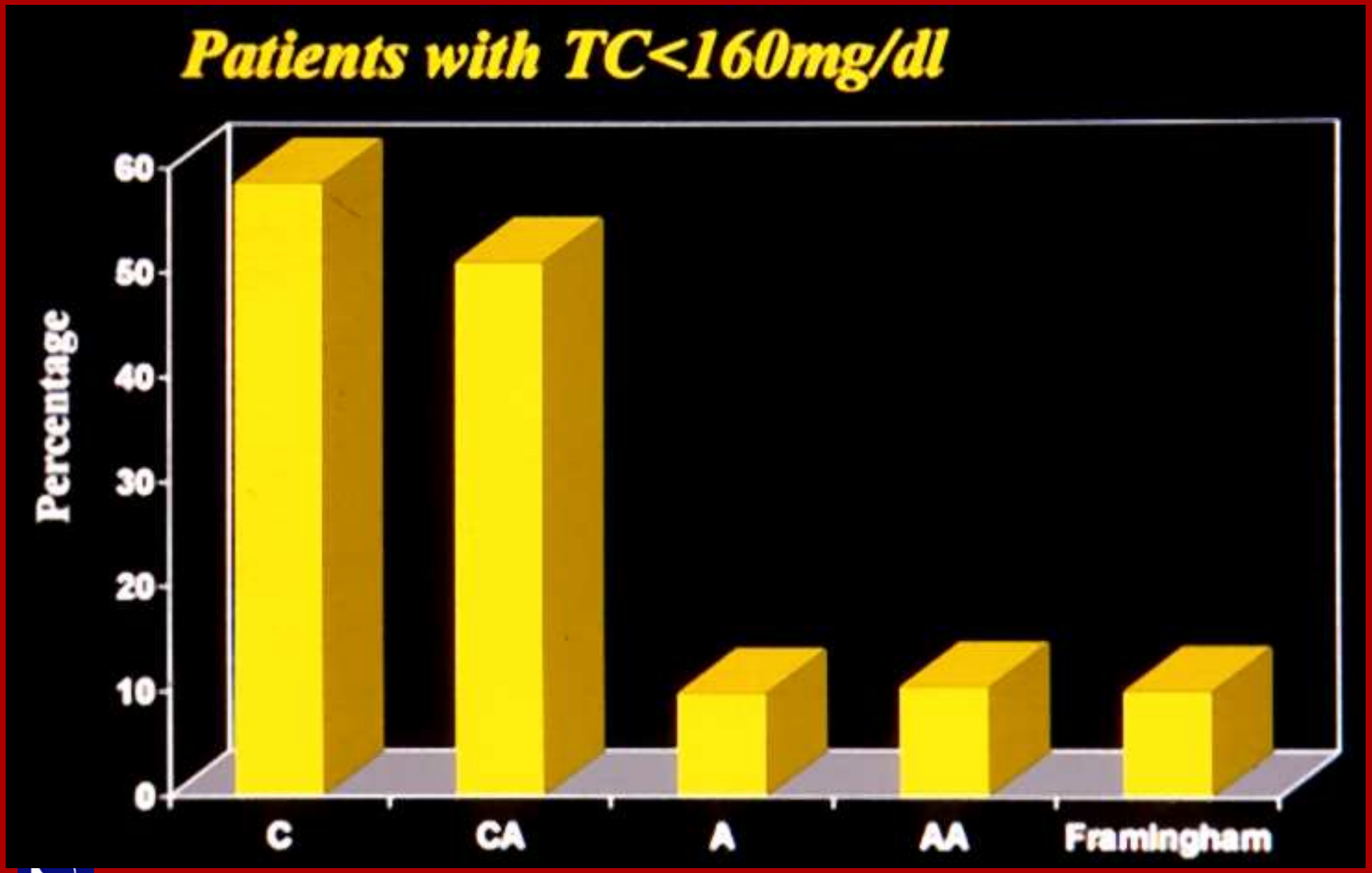
Hypoxemia

Upregulated nitric oxide

Increased bilirubin

Low platelet counts

CCHD UCLA Registry
Non-fasting Total Cholesterol



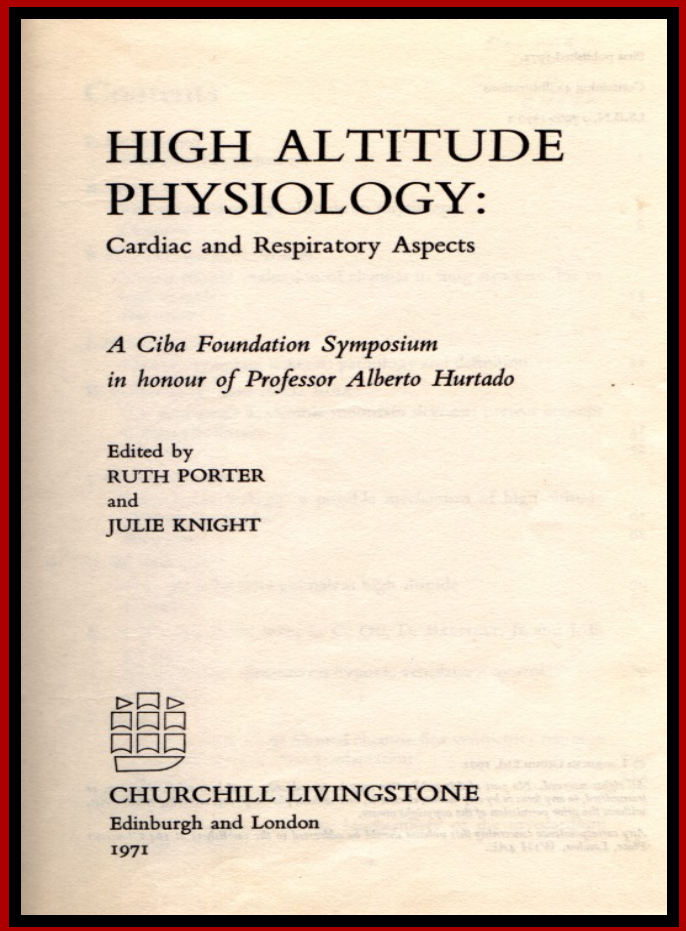
Hypocholesterolemia

Cyanosis & hypoxemia *are necessary but insufficient causes of hypocholesterolemia which tends to persist after surgical elimination of cyanosis.*

Cyanosis & hypoxemia *apparently provoke induction of hypocholesterolemic gene(s).*

High Living is Healthy

Altitude Favorably Affects Cholesterol Levels



HIGH ALTITUDE PHYSIOLOGY:

Cardiac and Respiratory Aspects

A Ciba Foundation Symposium in honour of Professor Alberto Hurtado

Edited by
RUTH PORTER
and
JULIE KNIGHT

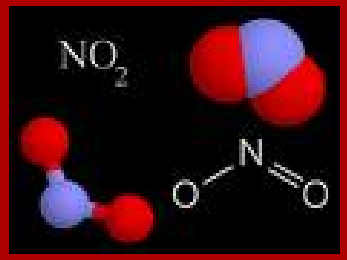
CHURCHILL LIVINGSTONE
Edinburgh and London
1971

Hypoxemic erythrocytotic adults acclimatized to high altitude have low levels of total cholesterol, low LDL cholesterol, elevated HDL cholesterol and dilated atheroma-free coronary arteries.

Antiatherogenic Effects of Hypoxemia

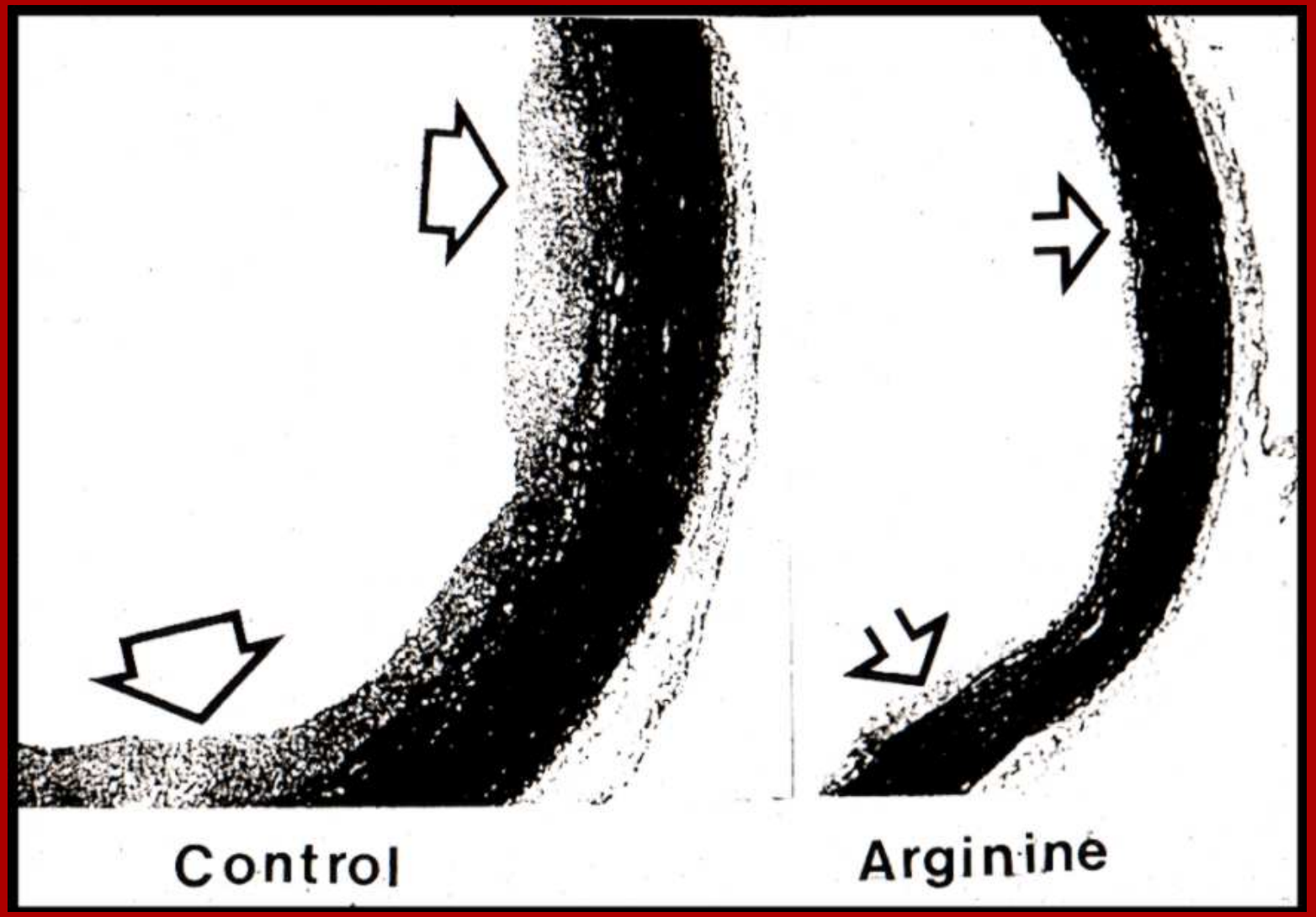
- *Hypoxemia is associated with reductions in oxidized plasma LDL and reductions in atherogenic oxidized intimal LDL.*
- *Larger LDL particles are relatively resistant to oxidation.*
- *Lack of small density oxidation-sensitive LDL behaves similarly.*

Antiatherogenic Nitric Oxide



NO is a paracrine molecule that inhibits platelet adherence and aggregation, stimulates disaggregation of preformed platelet aggregates, and inhibits monocyte adherence and infiltration.

Experimental Evidence of NO Effect



Bilirubin in CCHD

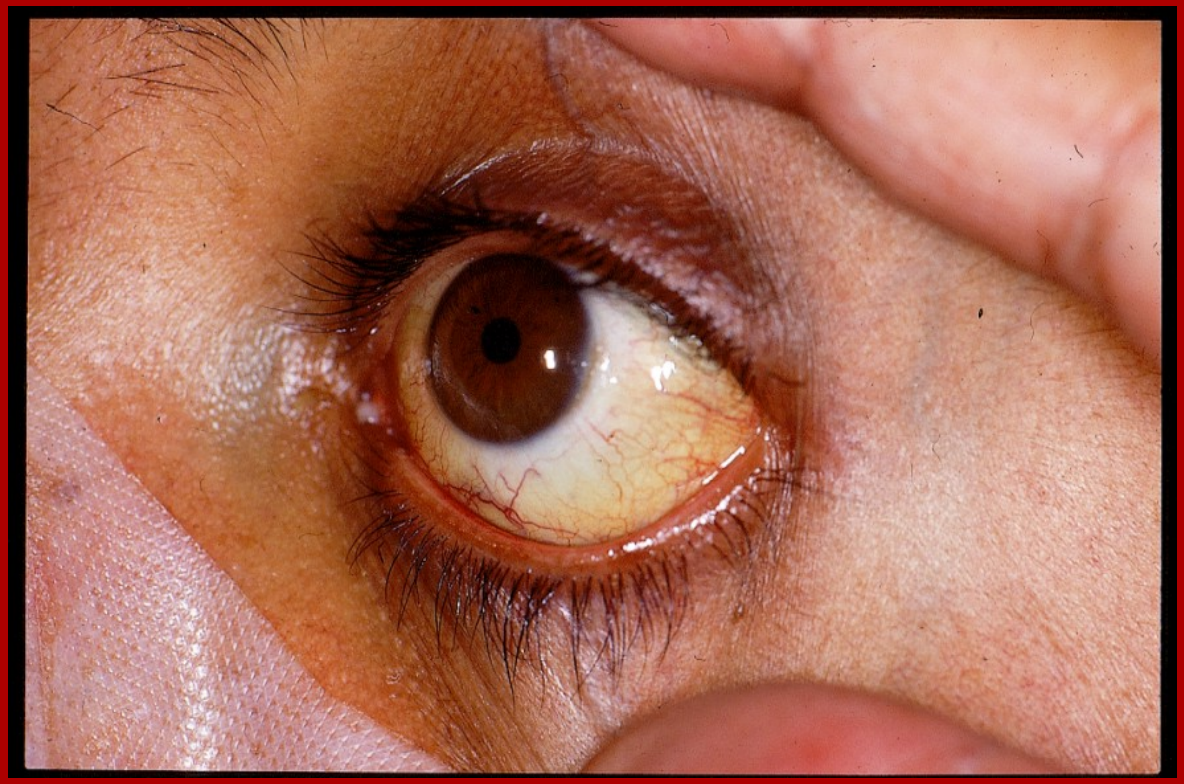
Typical levels of total bilirubin

CCHD

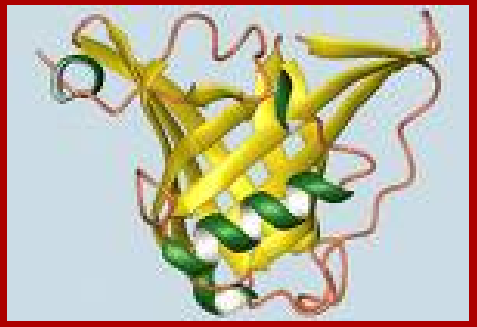
3.7mg/dL

Reference

0-1.0 mg/dL

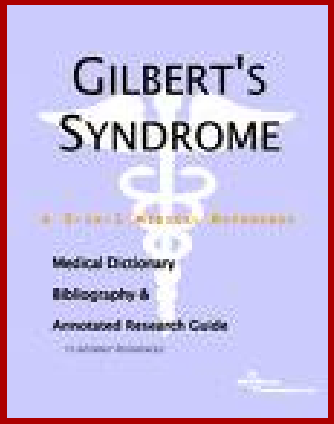


Bilirubin Kinetics



Bilirubin is formed from the breakdown of heme, a process that is excessive in the presence of the erythrocytosis of CCHD, and that coincides with a substantial increase in unconjugated bilirubin, a natural antioxidant that protects LDL cholesterol from oxidation.

Calcium Bilirubinate Gall Stones in CCHD



Gilbert's Syndrome

An Experiment of Nature

Gilbert's Syndrome is an inborn error of metabolism characterized by a benign elevation of unconjugated bilirubin with no liver damage or hematologic abnormality, but

with immunity from atherosclerosis.

Low Platelet Counts are Anti-atherogenic

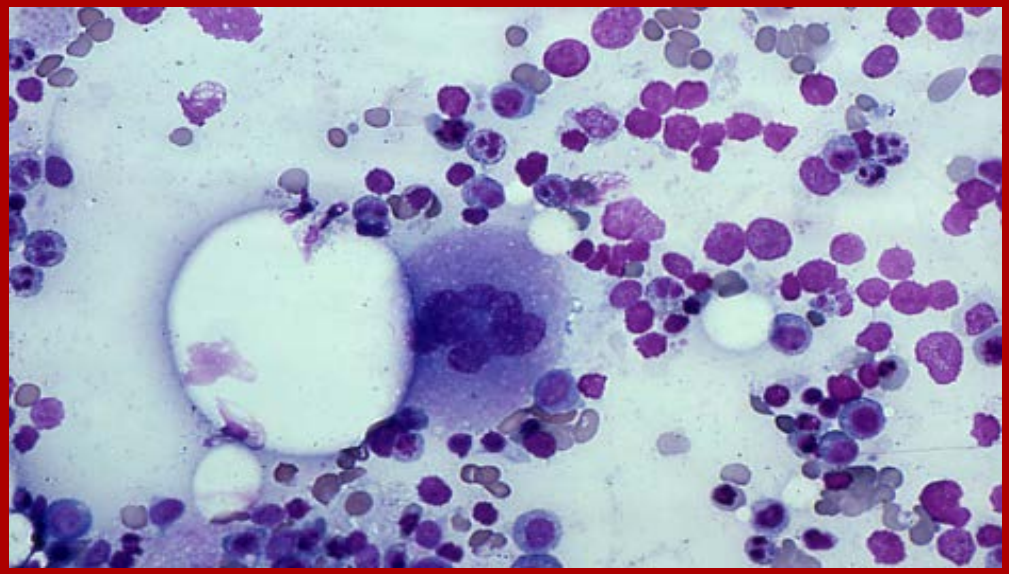
Platelet counts are low-normal or thrombocytopenic in CCHD because the shunted systemic venous megakaryocytes are deprived of their pulmonary transit, thus decreasing

platelet production in the lungs.

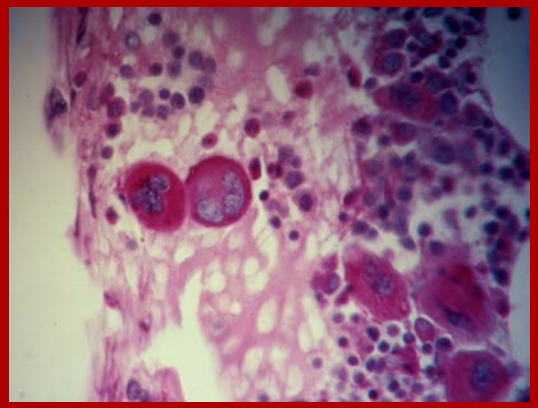
How Platelets are Formed

1) Whole megakaryocytes from the bone marrow enter the systemic venous circulation.
2) Platelets are formed by fragmentation of the cytoplasm of circulating systemic venous megakaryocytes during their pulmonary transit.

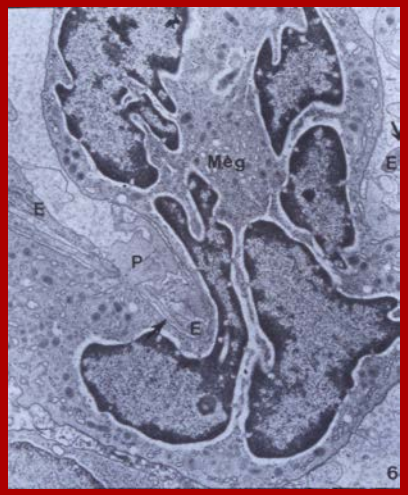
Marrow Megakaryocyte



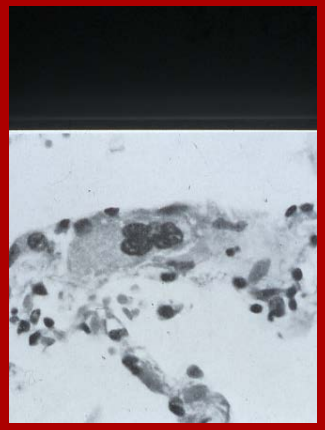
Megakaryocytes



In Bone Marrow



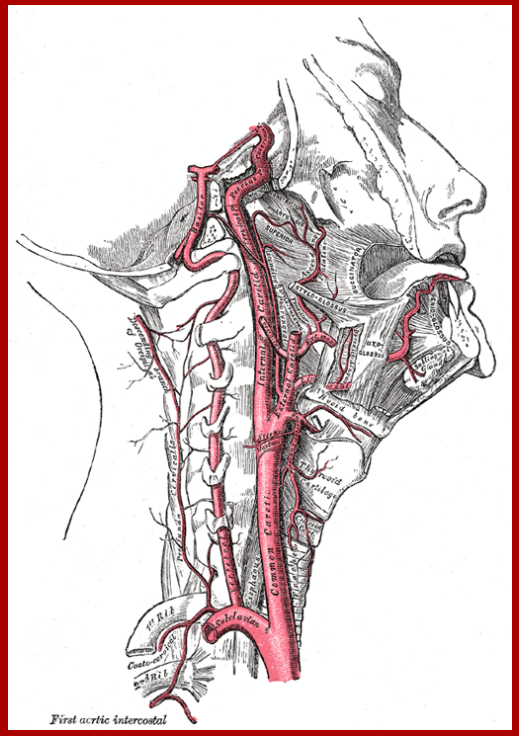
Leaving Bone Marrow



Lodged in a Pulmomary Arteriole

Perloff, et al Am J Cardiol 2000

Carotid Intimal Medial Thickness (IMT) as a Measure of Atherosclerosis.



Carotid IMT as determined by B-Mode ultrasound imaging is significantly decreased in adults with cyanotic congenital heart diseae.

The Coronary Circulation in Cyanotic Congenital Heart Disease
Conclusions

Extramural coronary arteries are dilated and tortuous because endothelial vasodilator substances act in concert with medial abnormalities to cause mural attenuation.

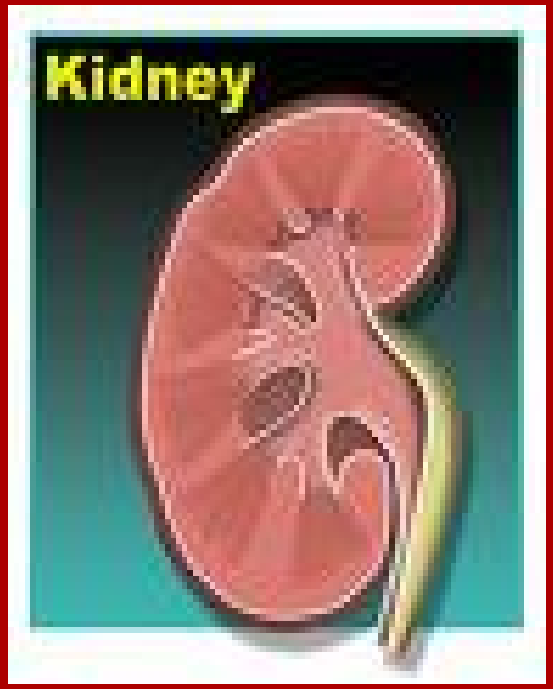
The Coronary Circulation in Cyanotic Congenital Heart Disease Conclusions

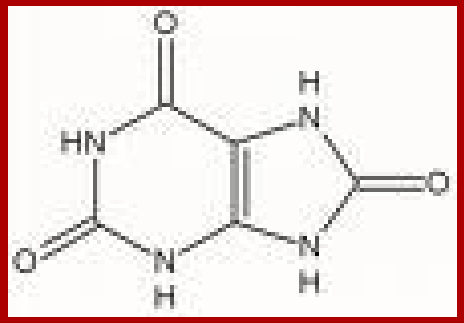
Basal coronary blood flow is increased in the dilated extramural coronary arteries, but flow reserve remains normal because the coronary microcirculation remodels.

Conclusions, cont'd

The dilated extramural coronary arteries are atheroma-free because of the combined anti-atherogenic effects of hypocholesterolemia, hypoxemia, upregulated endothelial NO, increased bilirubin, and low platelet counts.

The Kidney in CCHD

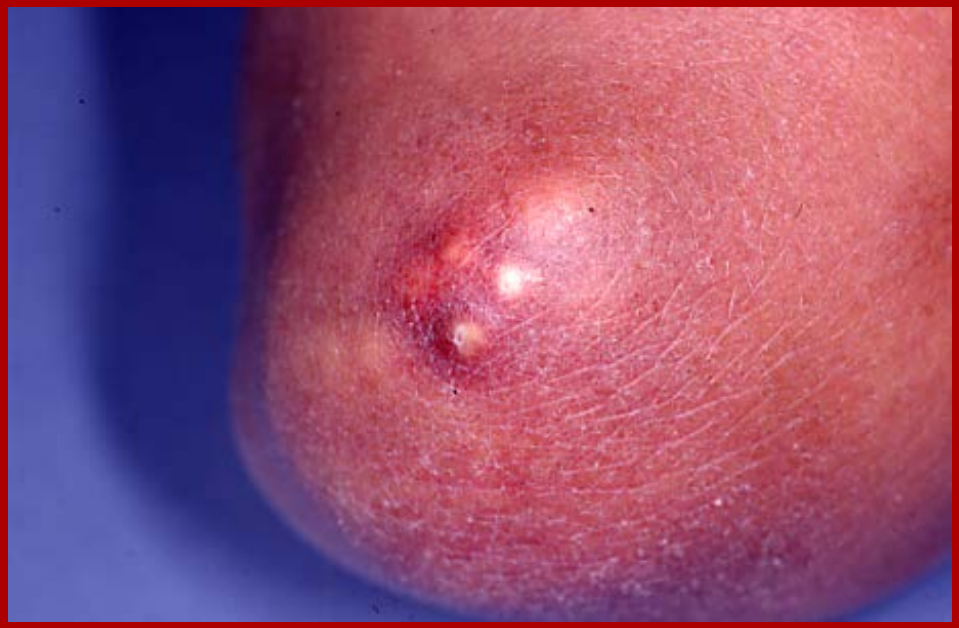




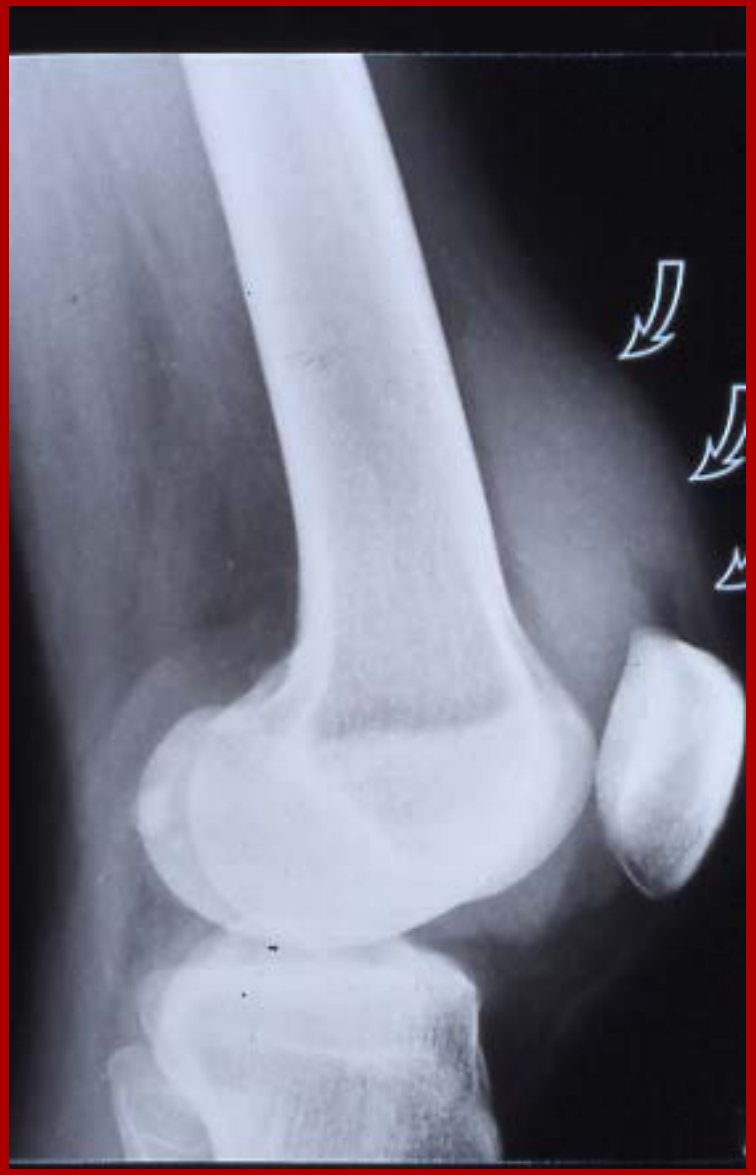
Hyperuricemia in CCHD occurs because of increased production and decreased renal clearance of uric acid.

Efficacy of long-term treatment of asymptomatic hyperuricemia is unproven. In the UCLA Adult Congenital Heart Disease Clinic, asymptomatic hyperuricemia is not routinely treated.

Urate Deposits



Painless Suprapatellar Effusion



Albuminuria

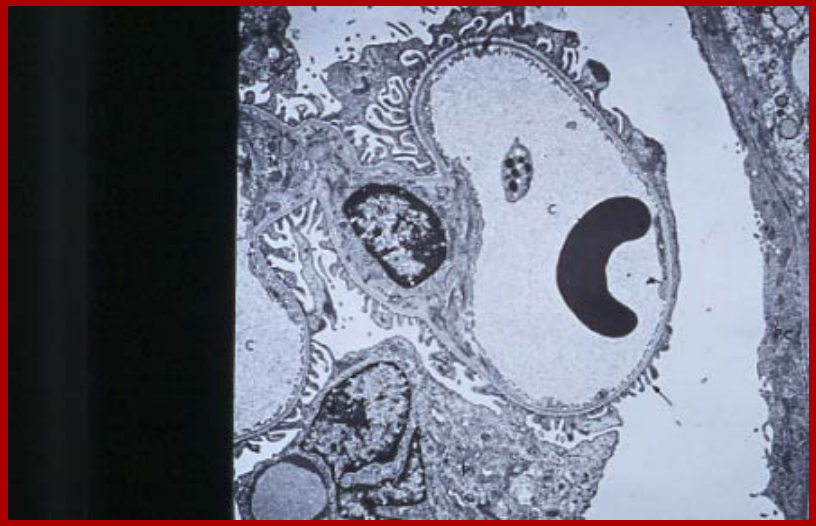
Glomerular capillaries are porous to albumin which is retained because the protein molecule is catatonic while the glomerular capillary wall is negatively charged.

The viscosity of erythrocytosis increases glomerular perfusion pressure and overcomes the cationic effect, so albumin leaves the glomerulus.

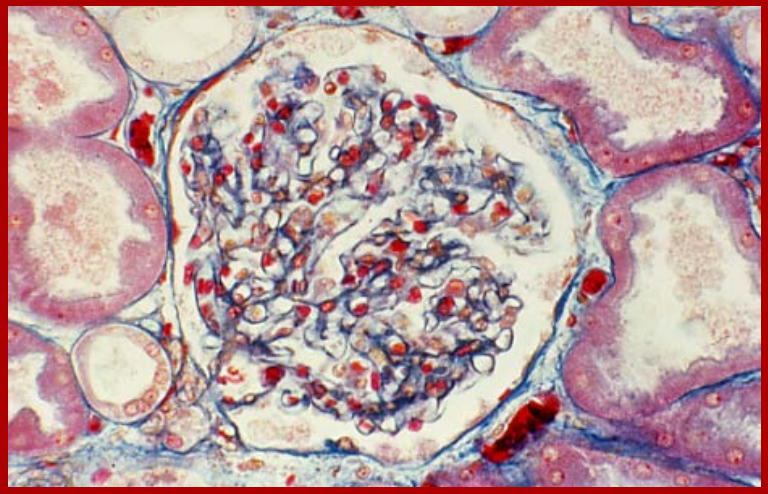
Glomerular Vascular Abnormalities in CCHD Nitric Oxide and the Kidney

NO is synthesized in the cytosol of mesangeal cells and glomerular capillary endothelial cells and functions as an autocrine hormone that modulates the glomerular response to increased perfusion resistance of erythrocytosis. Glomerular arterioles and capillaries dilate, and glomerular blood flow, vascularity and size increase.

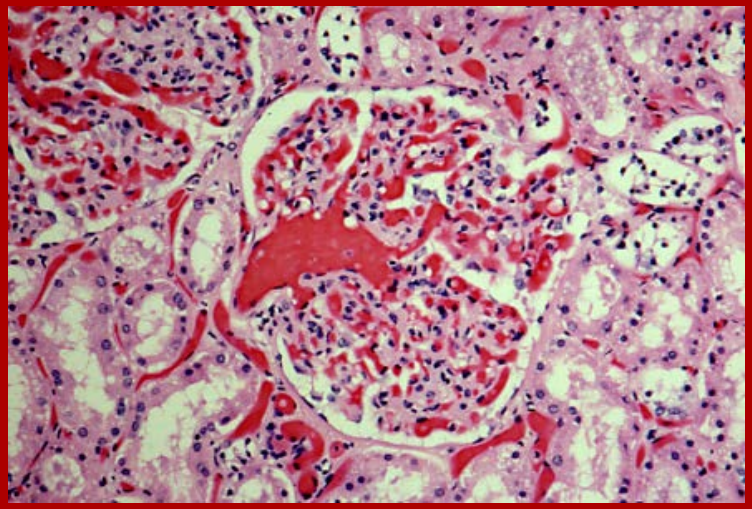
Normals



Electron Microscopy



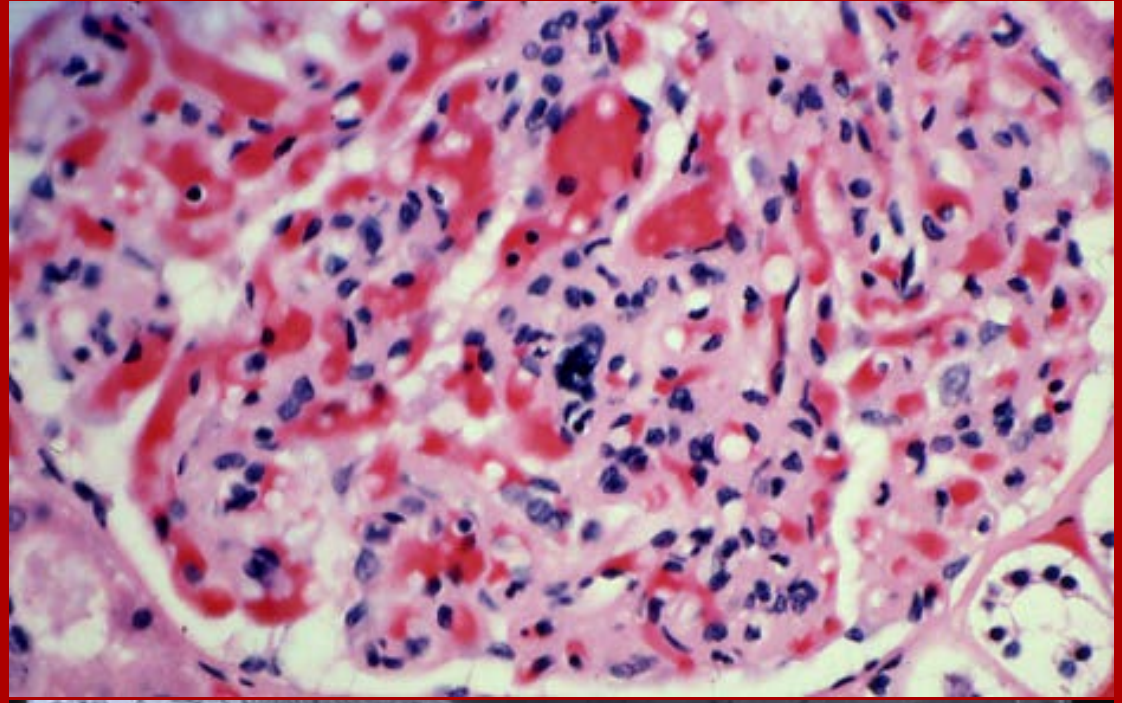
Light Microscopy

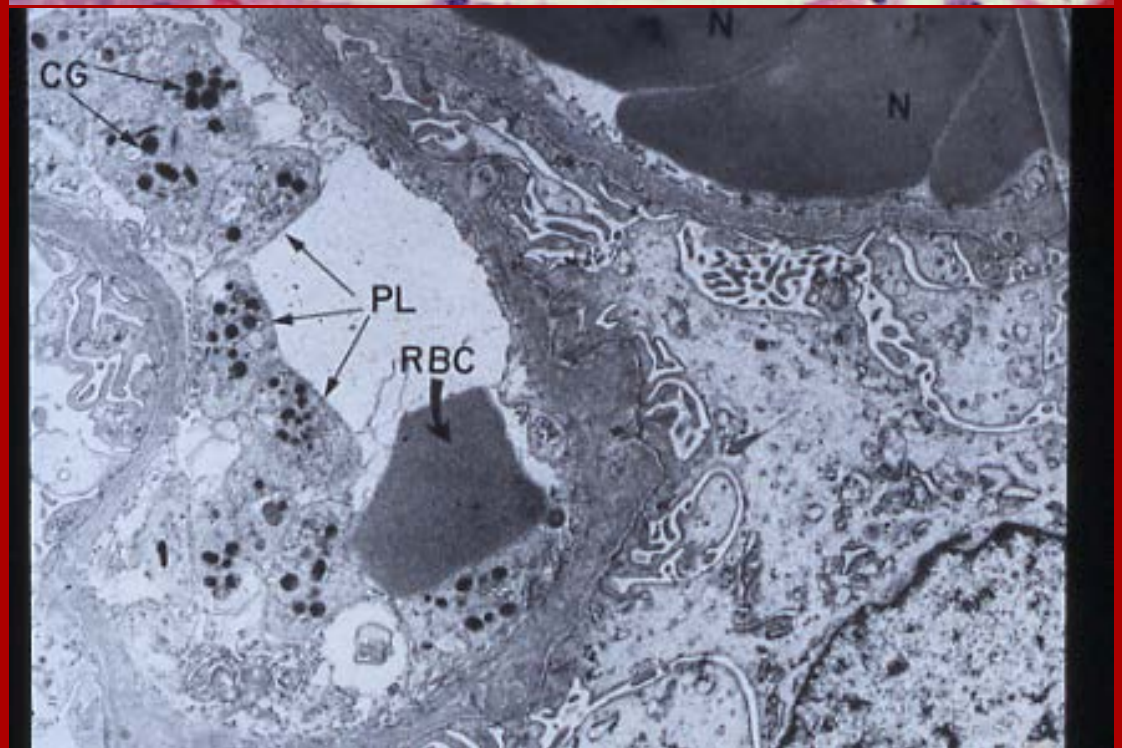


Hypervascular Glomerulus

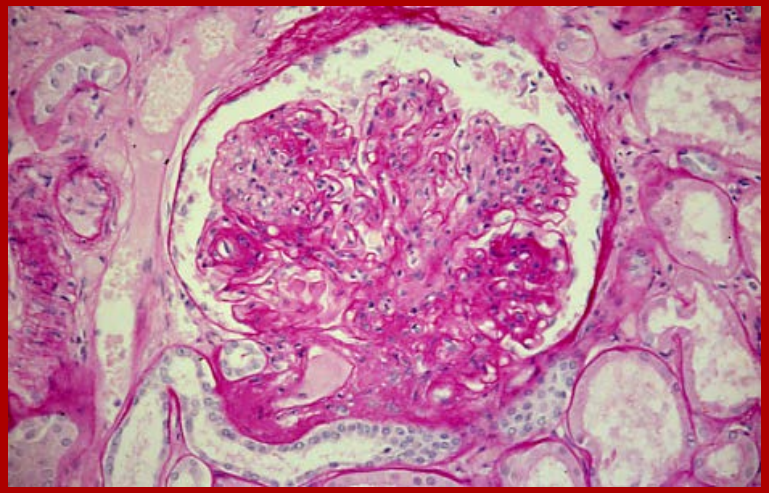
Shunted systemic venous megakaryocytes:

Light and electron microscopy.



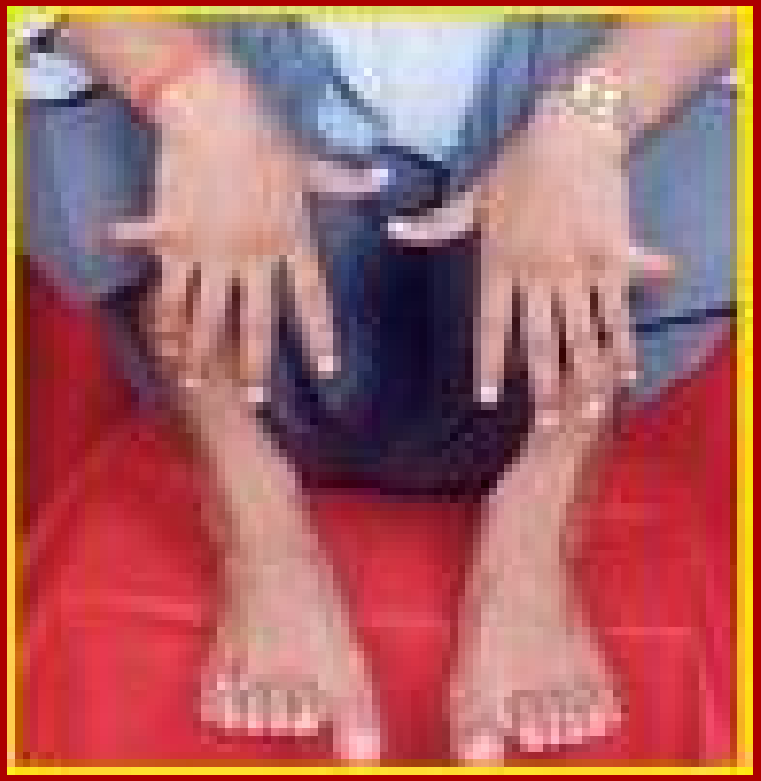


Nonvascular Glomerular Abnormalities

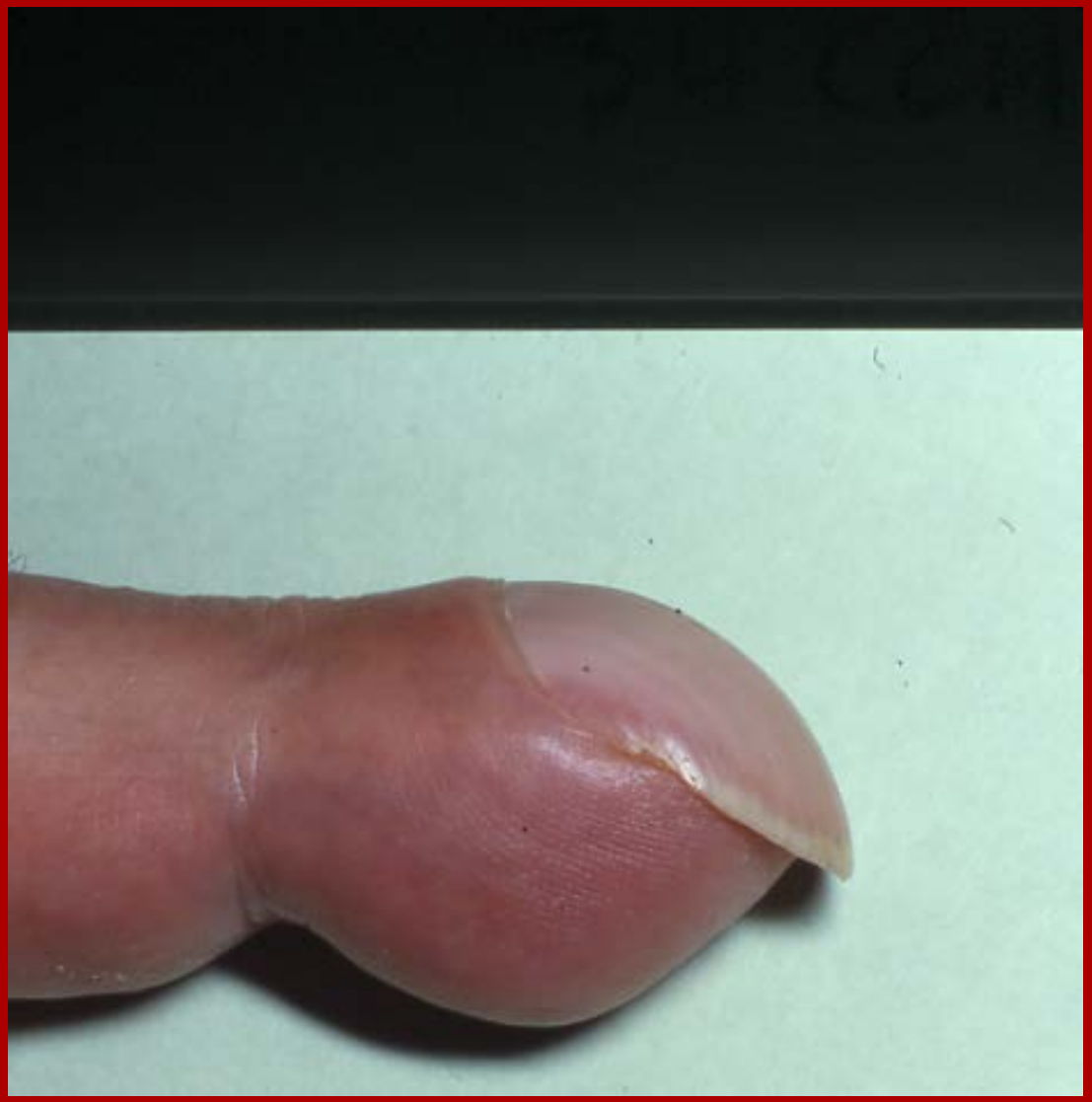


Shunted systemic venous megakaryocytes carry cytoplasmic PDGF and TGF beta to glomerular capillary beds. These mitogens and cytokines act locally because of their short half life, stimulating mesenchymally derived cells, enhancing connective tissue formation, and promoting protein synthesis, extracellular matrix, fibrosis and cell proliferation.

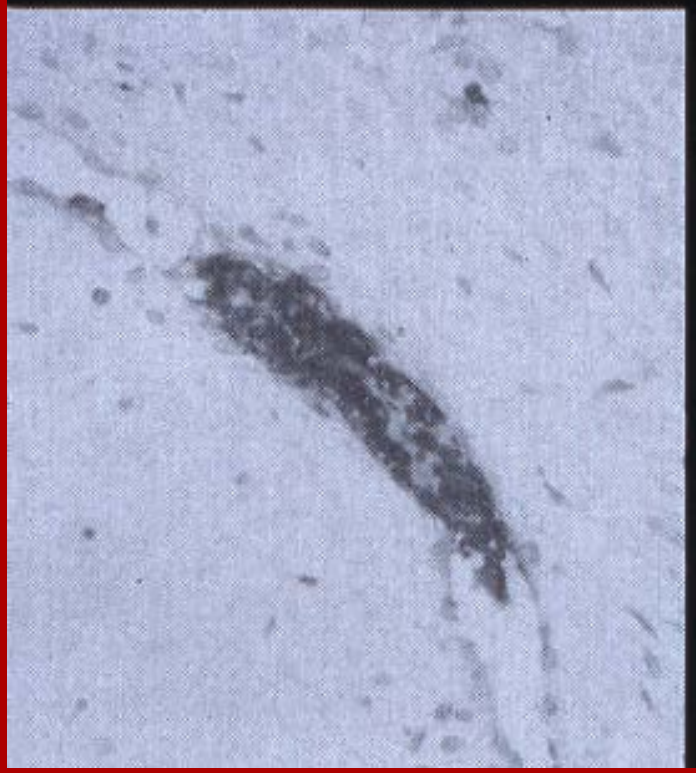
Digits and Long Bones



Clubbing & Osteoarthropathy

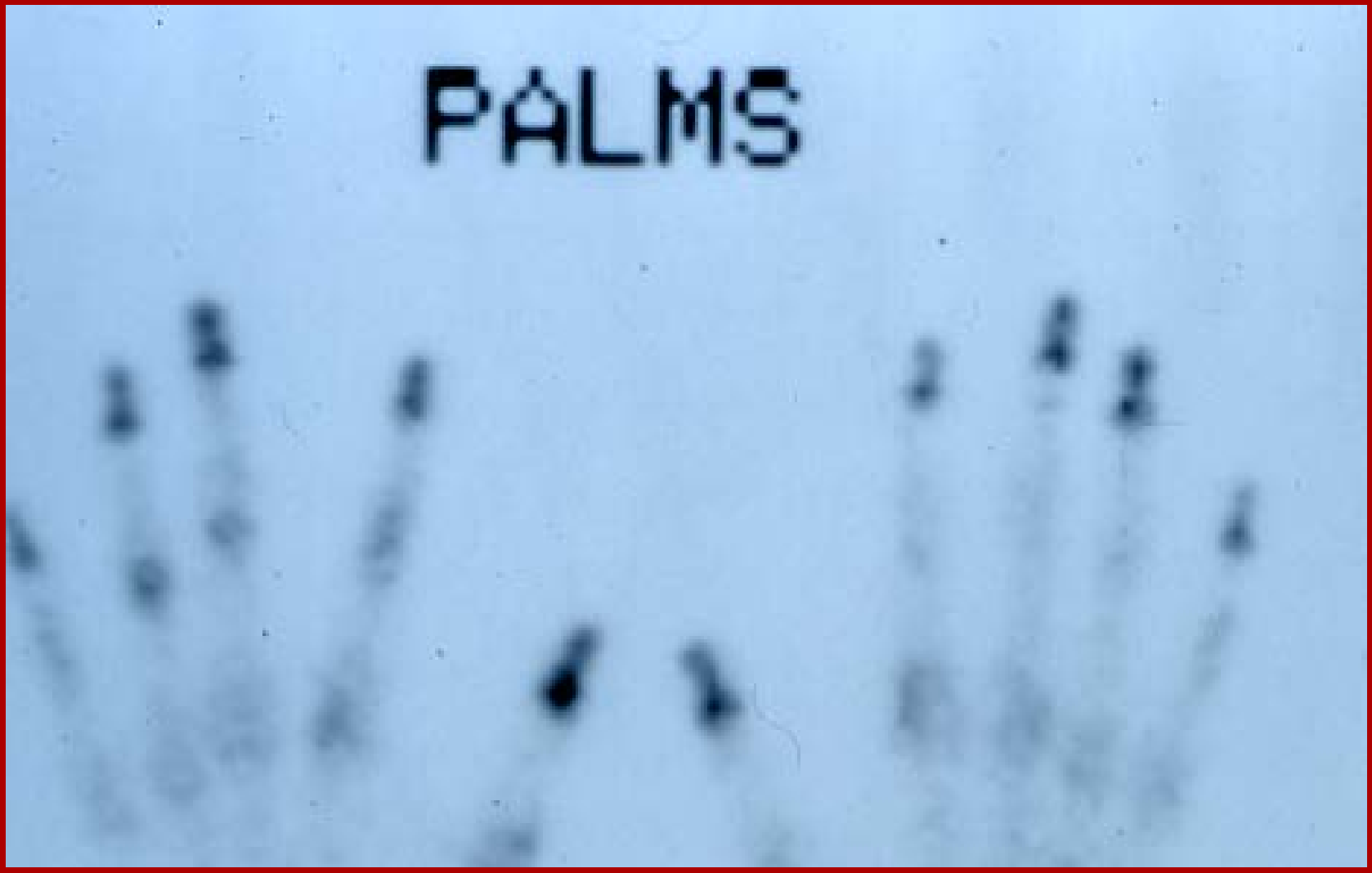


Fingertip Megakaryocyte
PDGF and TGF beta

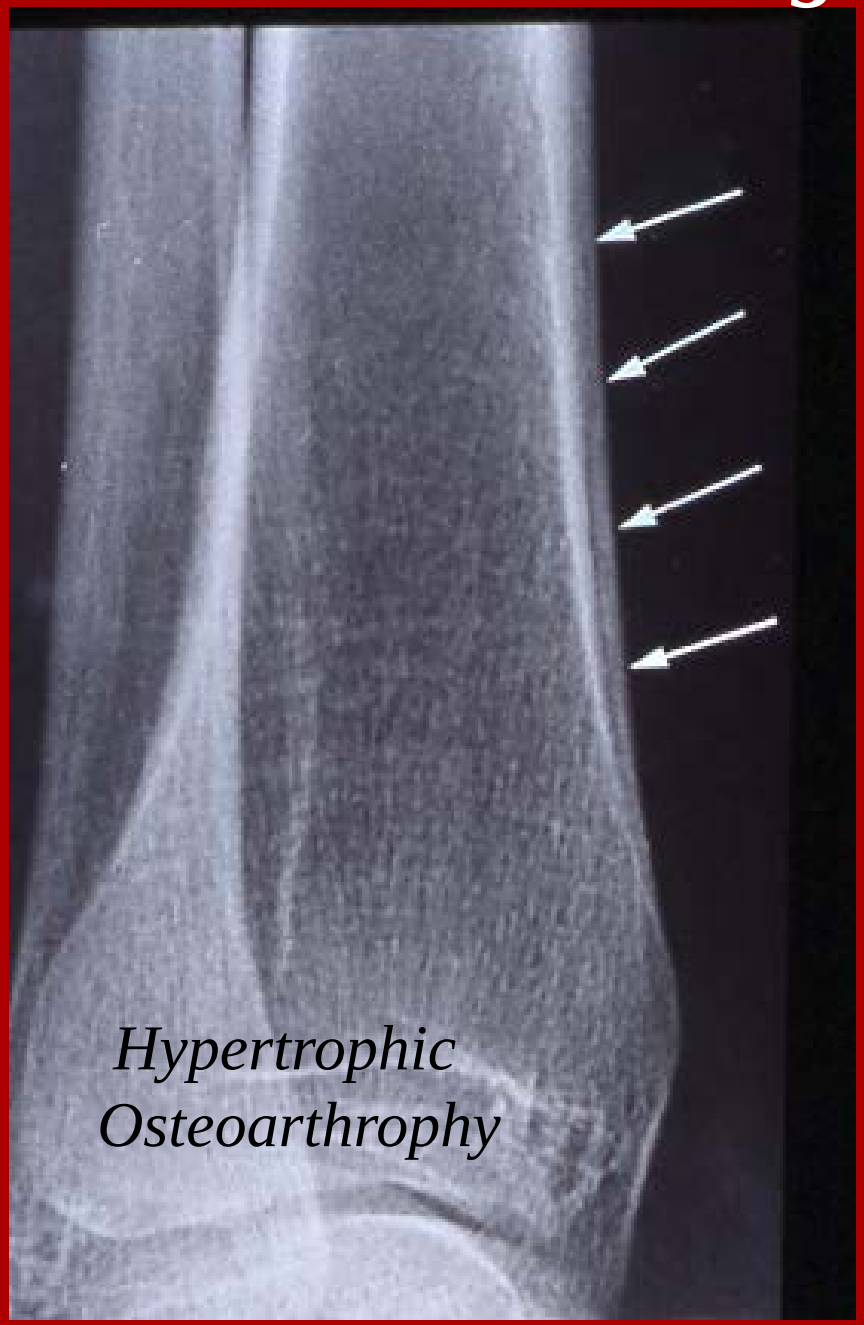


The Clubbed Digits

Technetium 99m Uptake



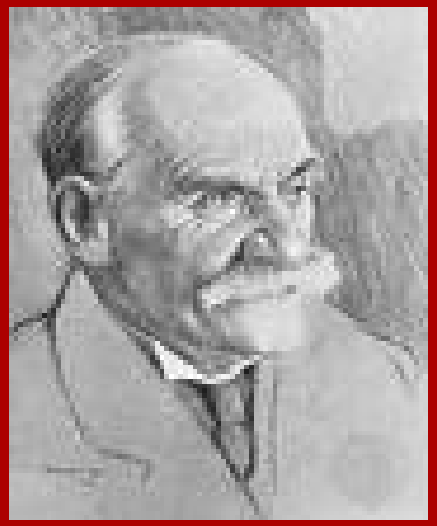
Long Bones



Hypertrophic Osteoarthrophy

Sub-periostial technetium 99m uptake

Respiration & Ventilation in CCHD



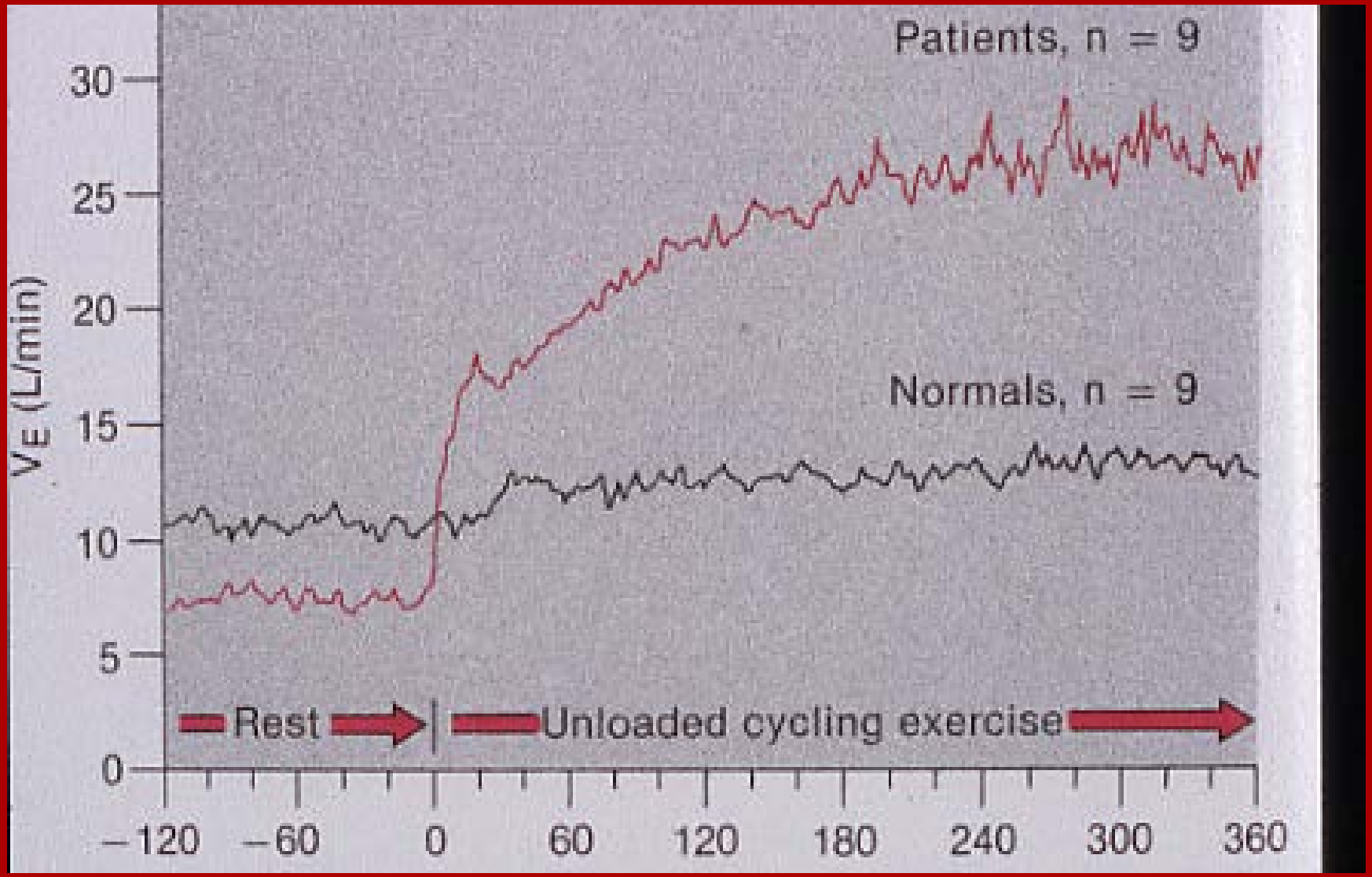
J. S. Haldane

In 1922, Haldane and Douglas placed a patient with cyanotic congenital heart disease in an oxygen-rich atmosphere and observed that the cyanosis persisted.

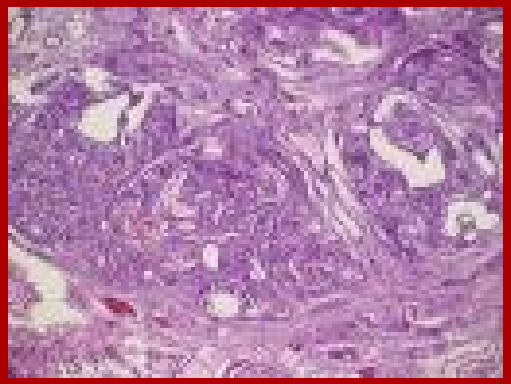
Dickinson W. Richards
1931

When the patient was placed in the oxygen chamber, the arterial oxygen saturation rose only 5%, scarcely more than the change that would occur in a normal person. Thus, the pulmonary alveoli oxygenated satisfactorily the blood that passed through them.

Response to Exercise



The Carotid Body & the Regulation of Breathing



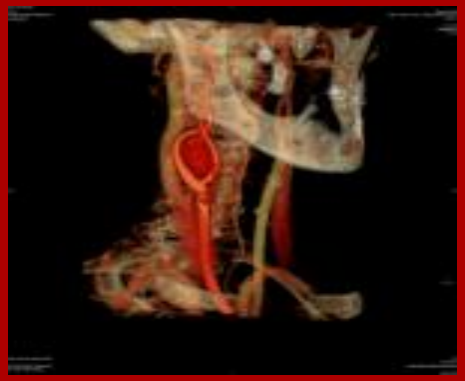
The carotid body is 4-5 mm oval nodule of chemoreceptor tissue involved in the regulation of breathing. It enlarges considerably in CCHD because of the stimuli of hypoxia, acidosis, and hypocarbia. However its chemoreflex ventilatory response is blunted.

Chemoreflex Ventilatory Responses at High Altitude

1) The blunted response to hypoxia and inhaled O_2 at high altitude are not reversed by descent to sea level.

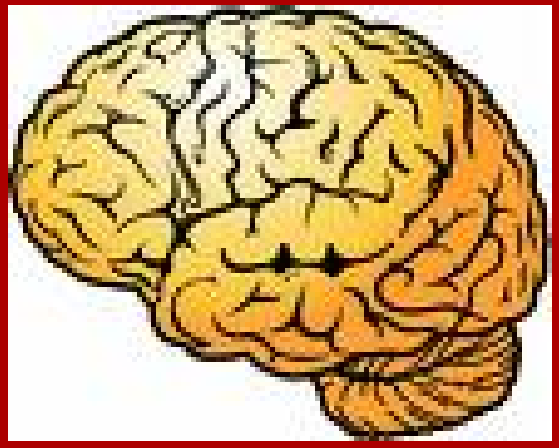
2) The blunted responses in CCHD after relief of cyanosis are being investigated.

CCHD--A Low Altitude Risk for Carotid Body Tumor

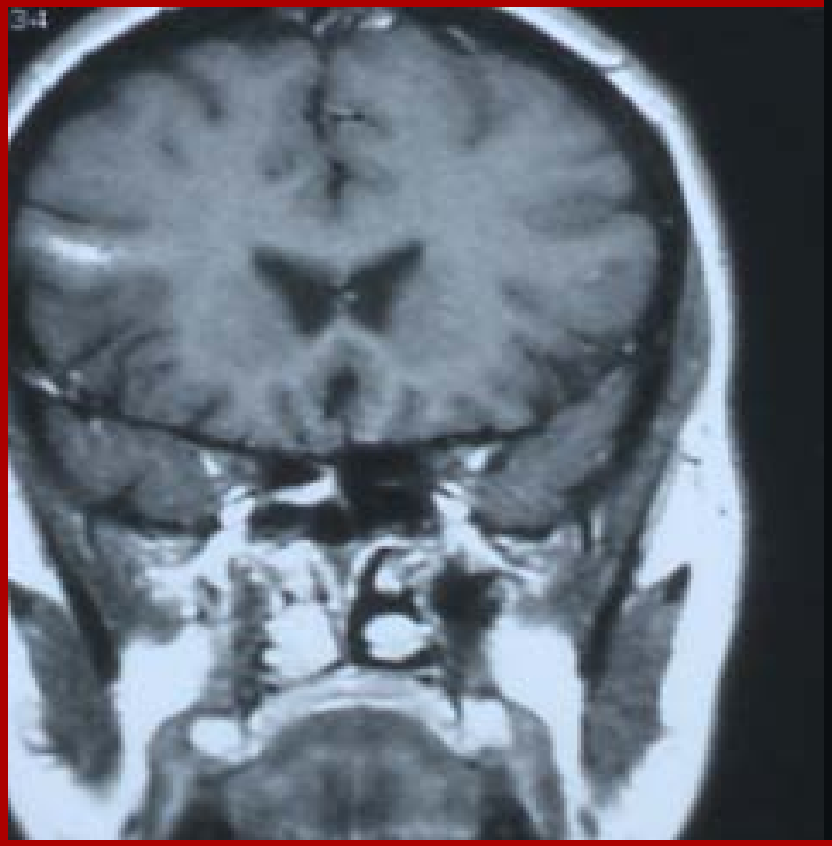


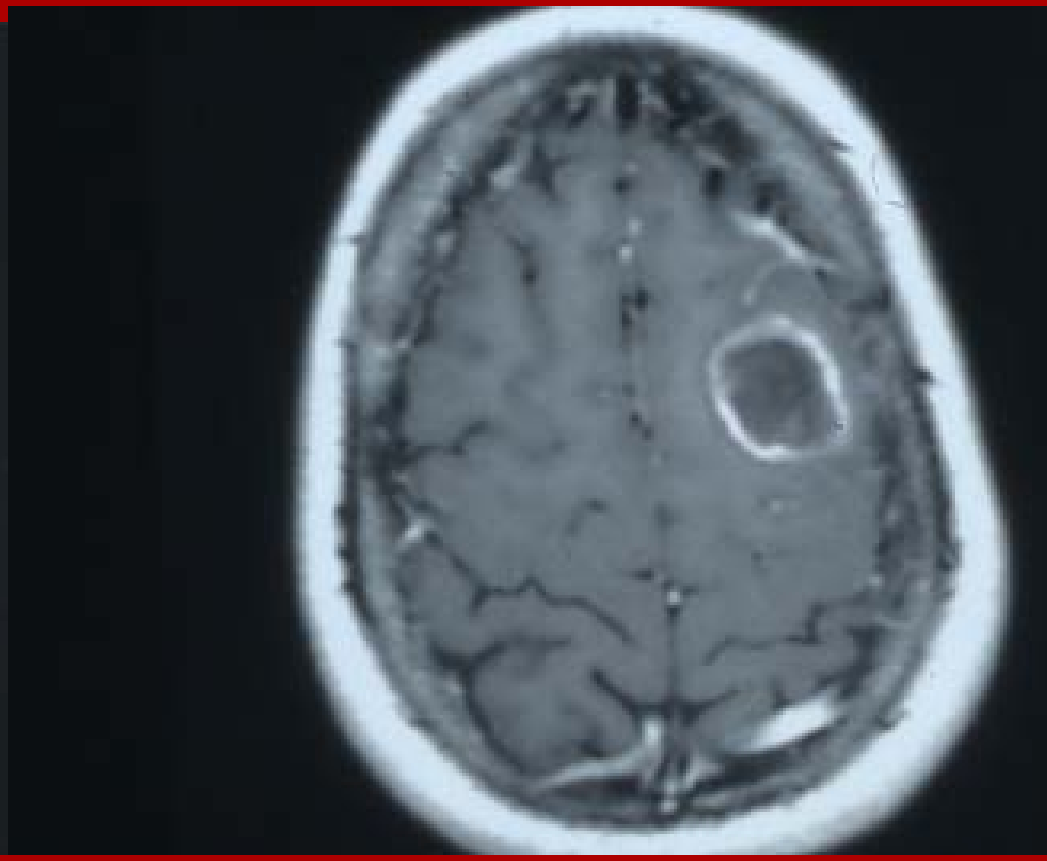
High altitude induces carotid body hyperplasia. Carotid body tumors are frequent among high altitude Peruvians, and have been reported in CCHD.

The Central Nervous System in CCHD



Healed & Fresh Brain Abcess





Healed

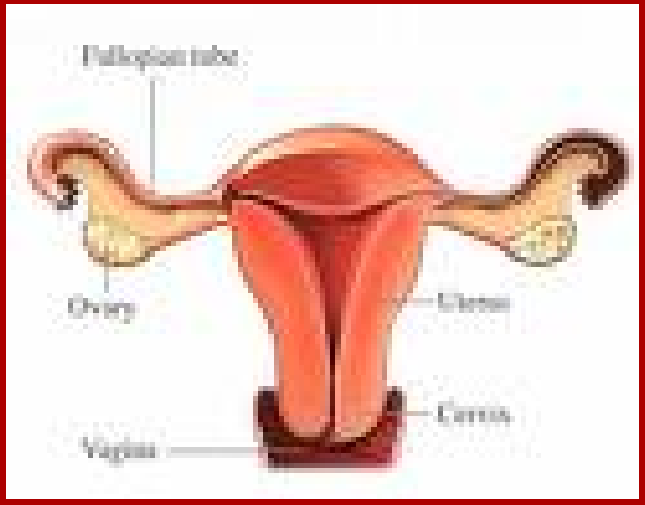
Fresh

The central nervous system and the cardiovascular system form almost simultaneously in early gestation. It is therefore not surprising that structural abnormalities of the brain accompany structural abnormalities of the heart.

Brain Volume in Fetuses With Congenital Heart Disease

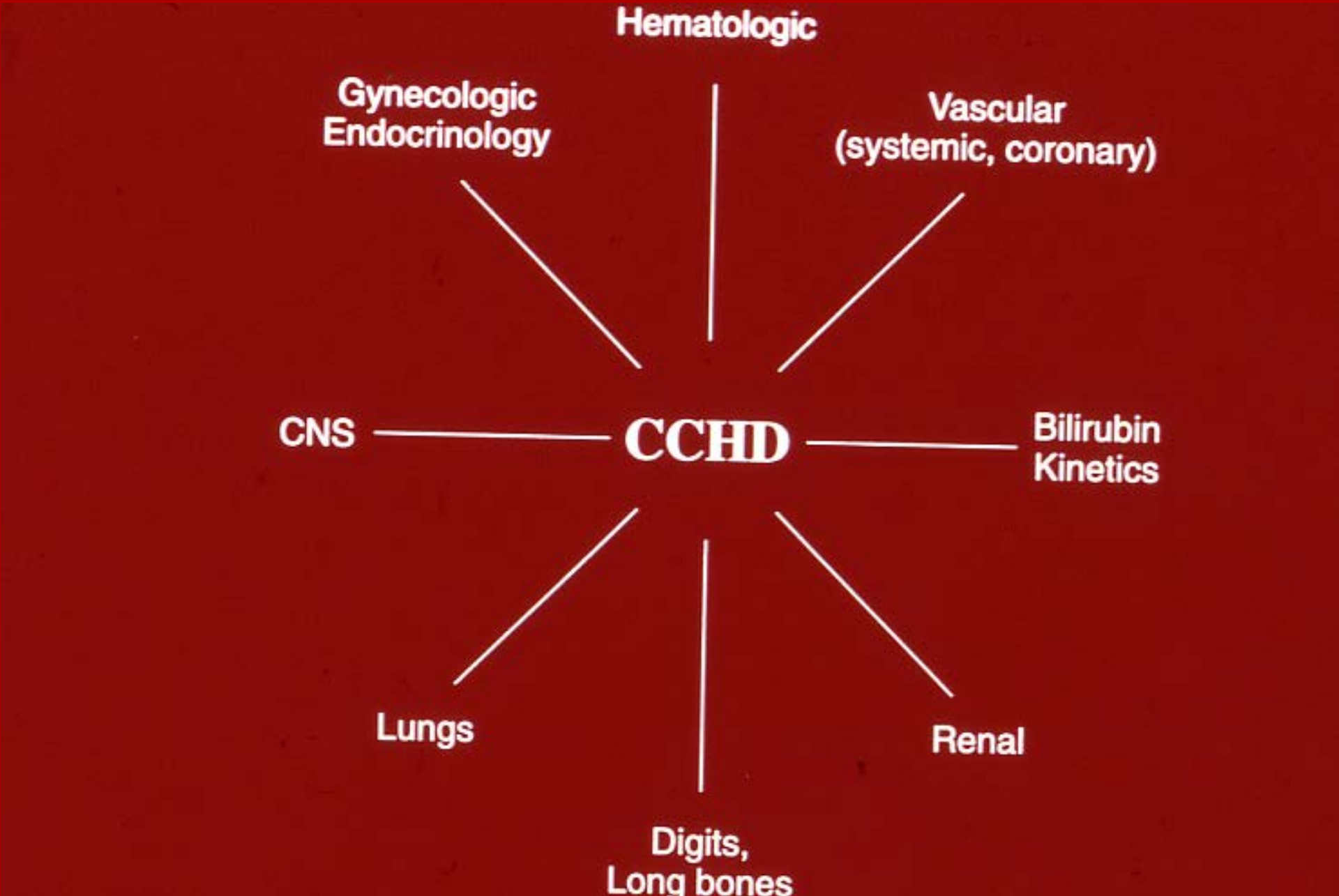
Third trimester fetuses with certain types of congenital heart disease have impaired neuro-axonal development and smaller than normal brain volumes adjusted for gestational age and birth weight.

Gynecologic Endocrinology in CCHD



Dysfunctional bleeding is common in females with CCHD, implying an anovulatory state with unopposed estrogen production and continuous endometrial stimulation that risks endometrial adenocarcinoma.

A Multi-System Systemic Disorder



Thank you